CANCER IN ONTARIO

1985

The Ontario Cancer Treatment and Research Foundation

87-01955/

The Ontario Cancer Treatment and Research Foundation was incorporated in 1943 by an Act of the Legislature of the Province of Ontario and reconstituted by The Cancer Act, 1957. The Cancer Act states that, "The object of the Foundation is to establish and conduct a program of research, diagnosis and treatment in cancer, including,

(a) the establishment, maintenance and operation of research, diagnostic and treatment centres in general hospitals or elsewhere;

(b) the transportation of patients and escorts to its treatment centres or to the hospital of the Institute for diagnosis, treatment or investigation;

(c) the establishment, maintenance and operation of hostels in connection with its treatment centres or the hospital of the Institute;

(d) the laboratory and clinical investigation of cancer problems;

(e) the co-ordination of facilities for treatment;

(f) the adequate reporting of cases and the recording and compilation of data;

(g) the education of the public in the importance of early recognition and treatment;

(h) the providing of facilities for undergraduate and postgraduate study;

(i) the training of technical personnel; and

(j) the providing and awarding of research fellowships."

Part II of The Cancer Act, dealing with The Ontario Cancer Institute, as amended by The Cancer Amendment Act, 1968-69, provides that the Institute Board shall consist of 15 persons appointed by the Lieutenant Governor in Council. Five members of the Institute Board shall be representatives of the Foundation, one of whom shall be the chairman of the Foundation. The Act specifies that one of the Foundation representatives on the Board of the Institute shall be the chairman of the Institute.

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CANCER IN ONTARIO

1985

THE COVER

Since 1972 the central motif for our covers has been the stylized outline of the Province of Ontario. Set in that outline are symbols representing the Foundation's eight regional cancer centres which, with the OCI/PMH, provide cancer-control services throughout the Province. To the people of Ontario, who provide the funds that make this work possible, the central message remains: "Wherever you are, the Foundation serves you". Understated in the lighter bars on the back cover, are some of the hundreds of individual services provided by a modern cancer control program. We hope *Cancer in Ontario* is providing a useful account of these services to the physicians of the Province, the interested members of the community -- especially our elected representatives -- and to other cancer control agencies in Canada and abroad.

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Toronto, Ontario, Canada
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MESSAGE FROM THE CHAIRMAN

Photo: Tony V. Hauser

1985 will be remembered as a watershed year. In August, the Provincial Role Study of Cancer Services in Ontario was completed and presented to the Foundation Board and the Minister of Health, the Honourable Murray Elston. When a summary of the study was presented later at a news conference, the public learned that the cancer control system in Ontario is in difficulty because of chronic underfunding dating back to the previous Role Study in 1972.

I am glad to report that substantial progress already has been made. The Ministry of Health has identified funds for the relocation of the London Regional Cancer Centre to the new Westminster Campus, for a major expansion of the Hamilton Centre, and for a new Centre in Sudbury to serve northeastern Ontario. On February 6, 1986, the Minister will preside at the official installation of a dual-energy linear accelerator in our Thunder Bay Regional Cancer Centre. This machine will provide a state-of-the-art radiotherapy service for northwestern Ontario.

The Ontario Cancer Registry continues to consolidate its position as one of the premier cancer data resources in the world.

It is with pleasure that I have accepted reappointment as your Chairman. Ms Isabel Rubin, as President of the Canadian Cancer Society Ontario Division, has joined the Board, and Mr. G. Ross and Drs. L. Siminovitch and B.M. Thall have graciously accepted reappointments. Also I wish to express my gratitude to Mrs. J.P. Morawetz and Mr. D.H. Hill upon their retirement after valuable service to the Board.

On behalf of the Board, I wish to record with appreciation the continuing support and dedication of the staff of the Foundation.

Finally, I wish to thank the Government of Ontario, the Canadian Cancer Society Ontario Division, the many patients, their families and their friends for the continued financial assistance we receive and without which our task would be impossible.

Michael A. Meighen
Chairman

THE EXECUTIVE DIRECTOR REPORTS

1985 has been a year of intense activity within the Foundation.

The Provincial Role Study of Cancer Services in Ontario has been completed and was submitted to the Minister of Health. Its 123 recommendations will challenge our vision; of these, the most prominent concern is the upgrading of space and equipment, an increase in operating resources, and specific organizational changes. In addition, the study recommended many changes in current programs, intended to enhance our service to patients, education and research.

In September 1985, the Foundation assumed responsibility for the Northeastern Ontario Oncology Program and established a medical oncology program at Laurentian Hospital in Sudbury under Acting Director Dr. R.E.T. Corringham. Planning continues for the construction of a centre designed to serve about 2200 new cases of cancer per year.

Planning is well underway to relocate the London Regional Cancer Centre and to expand the Hamilton Regional Cancer Centre, both by 1988. These centres have not been significantly upgraded since the 1960s. Further, it is becoming evident that our space in Ottawa and Toronto will require significant expansion.

The continuing increase in cancer cases referred to our centres – 34% in the past three years – has forced us to move to 10-hour shifts in radiotherapy at the Hamilton, Ottawa and Toronto-Bayview Centres.

To provide state-of-the-art radiotherapy, the Foundation has installed a dual-energy linear accelerator in Thunder Bay, and another is planned for Windsor in 1986.

The principal event in our research in 1985 was the maturing of the Ontario Clinical Oncology Group into a meaningful clinical trials vehicle. Over 500 patients have been entered into two trials and three further trials are in the planning stage.

The Foundation has appointed two new research scholars – Drs. J.E. Kudlow, Toronto, and G.F. Hammond, London, and two new career scientists – Drs. Susan Cole, Kingston, and R. Liteplo, Ottawa. An ad hoc committee, under the chairmanship of Dr. J.E. Till, has completed a major review of the Foundation's research program. As a result, the Research Committee has been replaced by a smaller Research Panel, which will be chaired by a Board member and have representatives from clinical, epidemiological and basic sciences with appropriate geographic and institutional representation.

The phone-in Cancer Information Service at the Hamilton Centre, jointly established and funded with the Canadian Cancer Society Ontario Division, continues to develop as a service to patients, the public and the media.

In 1985, several faithful employees have retired and new faces have appeared. Retirees include Dr. Stewart Lott, Director, and Dr. Winnifred Ross, radiation oncologist, of the Kingston Centre; Dr. A.F. Phillips, radiation oncologist, Hamilton Centre; Dr. William Allt, radiation oncologist, and Dr. John MacDonald, chief physicist, London Centre; and Dr. Wolfgang Hirte, medical oncologist, Ottawa Centre. To all I wish to record my thanks for a job well done.

In closing, I wish to thank all the members of the Foundation family and our many friends in the Canadian Cancer Society, the health sciences complexes, and the community at large for their continued support.

J. William Meakin, M.D., C.M., F.R.C.P.(C)
Executive Director

No annual financial statement is included in *Cancer in Ontario* but a copy of such statement will be provided upon request to the Head Office of the Foundation.

PROVINCIAL ROLE STUDY OF CANCER SERVICES IN ONTARIO: EXECUTIVE SUMMARY*

Overview

The Ontario Cancer Treatment and Research Foundation (OCTRF) and the Ontario Cancer Institute (OCI) commissioned this role study following agreement by the Ontario Ministry of Health. The prime motivation for undertaking the study was, and continues to be, the pressure for capital and operating resources necessary to prevent further deterioration of the existing system of cancer care in the Province, and to meet current and expected needs of Ontario cancer patients. The requirement for major capital development in space and equipment at the OCI (which incorporates the Princess Margaret Hospital [PMH]) was documented in internal and independent studies as long as 13 years ago. A previous provincial role study by Kates, Peat, Marwick & Co. recommended a major expansion of the OCI/PMH in 1972. The need at the OCI/PMH is now critical. A similar need exists at a number of OCTRF regional cancer centres.

The OCTRF and the OCI have served the population of Ontario extremely well. The study team believes the oncology system represented by these two organizations is essential for the future. Without it, optimal and efficient cancer care, in our view, will not be achieved in the Province. Both organizations are guided by an important principle: Exemplary clinical care can only be provided through a close integration with research and teaching. Throughout the world, contemporary successes in cancer care are often attributed to the application of this principle. Its application in Ontario makes aspects of the comprehensive cancer control programs offered by the OCTRF and the OCI a model for others.

Nevertheless, the present system cannot hope to match past performance under current resource allocations and organizational arrangements. Cancer incidence is increasing rapidly as our society ages. Over the period 1974 to 1984, while the Ontario population grew by 16%, the number of new cases of cancer increased by 37%. During this decade of growth, important components of the system, notably the OCI/PMH and some OCTRF regional cancer centres, did not receive the funding required to correct deficiencies identified many years ago. Looking to the future, the expected number of cancer cases 10 years from now (1994) represents a further 47%

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*Reprinted, with minor revisions, from the report entitled PROVINCIAL ROLE STUDY OF CANCER SERVICES IN ONTARIO FOR THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION AND THE ONTARIO CANCER INSTITUTE, prepared by Currie, Cooper & Lybrand, and the RMC Resource Management Consultants, Ltd., Toronto, Ontario.

increase while the population is expected to grow by only 12%. Existing resources are inadequate in quality and quantity to cope with present demands, let alone future needs, and are deteriorating. Substantial additional funding must be provided immediately.

The ability of the Province to plan and implement an effective cancer control program to meet future needs is in jeopardy. The excellence, which characterized the system of cancer care in Ontario in the past, and which was built up at great cost with dedication, effort and goodwill, is being lost.

An increasingly complex, competitive environment in the health care system at large is fragmenting efforts to provide a coherent, province-wide program of cancer control that includes prevention, diagnosis, treatment, research and education. The organization of cancer control in Ontario and the resources allocated to it need to be reconsidered. Otherwise, destructive competitive forces will fragment the existing cancer system; currently overtaxed resources will not meet future needs and will deteriorate beyond the point at which they can still be salvaged; and access to specialized care for cancer patients will correspondingly decrease. Patients seeking cancer care will more frequently turn to individual physicians and hospitals outside the OCTRF and the OCI, increasing costs and pressure for service throughout the Province. In our view, the care that will be provided as a result will neither be as effective nor as efficient as if it were offered in conjunction with a system based on the OCTRF and the OCI.

An effective program of cancer control without a specialty base is simply not possible because of the complexity of cancer and the methods used to treat it. Present requirements are for sophisticated diagnostic and treatment equipment and techniques. A critical mass of highly trained medical, scientific, and technical staff is necessary to create a close link between treatment, audit, clinical trials, and basic and applied research. These requirements contribute to assure adequate standards and effectiveness of treatment. They cannot be met through the present general hospital system alone.

An unco-ordinated, fragmented system involving selected hospitals as oncologic specialty bases also cannot offer a cancer control program effectively and efficiently. Not only must its components compete for very scarce and expensive human and technical resources, they must also compete for patients to maintain program standards and viability. For many cancers the number of patients seen in the selected hospitals of an unco-ordinated system could be quite small and no particularly specialized skills and knowledge would be developed, compared to that achieved within the OCTRF/OCI*.

Future requirements will only increase the need for a co-ordinated oncologic program in the Province. As noted by one of our international advisors, improved knowledge of cancer biology, notably in the areas of drug resistance, monoclonal antibodies, neovascularization of tumors, the nature of metastases, and genetic alterations, which exist between normal cells and cancer cells, is expected to lead to the introduction of additional but fundamentally new approaches to cancer management within the next decade. A province-wide system, based on the OCTRF and the OCI, together with a co-ordinated network of interested and committed physicians in the community, would be the best way to disseminate such new knowledge. A co-ordinated system would also encourage establishing and maintaining adequate standards, treatment effectiveness and efficiency in a high-cost environment.

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*The designation "OCTRF/OCI" rather than "OCTRF and OCI" or other forms is used for brevity, and to emphasize the "system" these two organizations constitute.

The potential benefits of an effective provincial cancer control program are extensive, particularly in view of the chronicity of cancer. New advances promise improved techniques for prevention and early diagnosis, and improved cure rates for patients with advanced malignant disease. (Expected results are more cancer cases prevented and more productive years of life of greater quality saved.)

This study strongly recommends that two steps be taken. First, sufficient resources must be provided to correct the deficiencies which have resulted from underfunding over the past decade. The capital funds required will be in the order of $100 million for facility upgrading and replacement, and another $50 million for equipment over the next 5-7 years plus an appropriate increase in operating budgets. This will not only allow the system to meet the current needs of patients but it will raise morale of the staff, attract qualified health care workers to the system, and encourage the acceptance of a concept of regionalization and co-ordination throughout the Province. Our second recommendation is that, after the first step has been established, the OCTRF and the OCI should merge into one unified organization under a single Board. The new organization should be responsible for a broad cancer control program ranging from prevention to long-term care, in a province-wide, co-ordinated clinical service with an expanded role in research and teaching. This new organization must preserve the strength and excellence of the OCI, nurturing at the same time the new and growing capabilities of the regional cancer centres.

Correcting funding deficiencies of both organizations before merging the OCTRF and the OCI under a single Board is important for four reasons. First, the urgency is greater. Second, the Boards and staff of the OCTRF and the OCI are so preoccupied with their funding needs that their attention and co-operation in the extensive work, which will be required to effect organizational restructuring, is not likely to be given sufficient priority until their funding problems have been resolved. Third, both the OCTRF and the OCI will want to negotiate their entry into the new, unified organization from positions of strength, knowing that their financial needs are secure. Fourth, the OCI is at greater risk than the OCTRF, in that its funding needs are much larger than those of any one centre. Thus, if relatively modest funding is provided sufficient for one or more centres, but insufficient to permit redevelopment of the OCI, or if funds are provided in small amounts over a period of years, the OCI will be disadvantaged relative to the OCTRF. The OCI's legitimate concern must be recognized and met. For these reasons, correcting past funding deficiencies of the OCTRF and OCI and providing for future needs must receive top priority and the funds must be committed or assured before the merger proceeds.

We must emphasize the need to preserve the strength and excellence of the OCI/PMH. As the only provincial cancer hospital, it has been and remains the flagship of the Ontario oncology system. At the regional level it has set high standards in service to patients, in research, in the integration of research and service, and in education, particularly in providing a high proportion of radiation and medical oncologists for the service needs of the Province and Canada.

The provincial cancer system has benefited greatly from the strength of the OCI. The growth and development of the OCTRF centres towards regional comprehensive cancer centre status with international standards has been significantly aided by the example of the OCI.

Everything that has been gained by the development of the OCI over the last 25 years is at risk of being lost. There is a critical mass of selected and dedicated scientists and physicians at the OCI. Their achievements are greater than expected from the sum of the individuals. Such a critical mass, directed to excellence by consensus and tradition, is difficult to develop and maintain. If the environment is not supportive, staff will quickly move elsewhere. This is already occurring. The loss of a critical mass of high-quality staff from the OCI would have a profound effect on its current role. Provincial services to patients would be compromised, both through a lowering of standards and the deterioration of the professional training programs which are the most extensive in the country.

The Ontario cancer system stands at a crossroads: With support from the Province, it can proceed toward improved system effectiveness, gaining long-term benefits for a public that will increasingly experience cancer as a disease; or, in the absence of support from the Province, it will proceed toward deterioration and limited capability to serve real needs. The road taken will be determined by decisions made on the allocation of additional resources. If such allocations are made, the degree of progress along the road to a truly effective cancer system will be determined by its future goals and organizational structure.

Characteristics of the Provincial Cancer System

Cancer is the second most common cause of death in Ontario. It is pervasive. Estimates suggest one in four persons will develop cancer during their lifetime and two out of three families will be affected by the disease. With an increasing population that is also aging, and in the absence of specific preventive measures, we will continue to see cancer incidence rise; no "magic bullet" cure, despite recent advances in treatment and research, is likely to change the pattern in the immediate future.

Cancer patients in Ontario obtain treatment and care from two sources. Approximately 50% are seen by staff of the OCTRF/OCI system at seven OCTRF regional cancer centres and at the PMH. The OCTRF centres offer ambulatory cancer care; the PMH is the only Ontario cancer hospital with both inpatient and ambulatory care capabilities. The remaining 50% are seen only by physicians currently practicing outside the system in private offices and the general acute care and chronic hospitals. Most of the interventions for these patients involve surgery and, increasingly, chemotherapy.

The OCTRF/OCI constitutes the formal cancer system in the Province. The system is mandated by The Ontario Cancer Act, which defines the composition of the Boards of each organization, together with their objectives. The OCTRF regional cancer centres and the OCI/PMH are the exclusive sites of complex, expensive radiation therapy equipment. They are the bases for specialized, highly trained manpower in oncology. It is from these locations and from the Head Office of the OCTRF, together with the administration of the OCI, that extensive province-wide cancer control programs are conducted. The programs involve all medical nursing, and scientific disciplines related to cancer and medical care. Consultants collaborate with staff of the OCTRF/OCI to deliver care not only at the OCTRF/OCI centres, but also at other hospitals and health care facilities. Operative surgery is not done within the centres or the OCI except for endoscopy, minor biopsy procedures and the use of intracavitary or interstitial radioactive sources.

The origins of the current system lie in the report of the Cody Commission of the 1930s and in subsequent developments in the following two decades: First the establishment of the OCTRF, then the OCI. The basic premise of the Cody Commission was that centralization of expensive and complex radiotherapy equipment in regional clinics that had an association with a medical school would not only contribute to more effective and efficient treatment programs, but would also generate an appropriate milieu for research. This premise remains applicable today for radiotherapy and has important significance for chemotherapy.

Past Accomplishments

The OCTRF/OCI system has served cancer patients of the Province extremely well. It has set high standards in the quality of oncologic care and efficiency in the use of staff, space and equipment. This has meant centralization of services, particularly for radiation therapy. Through outreach programs and interactions with other physicians and hospitals, the objective of providing care as cloes as possible to a patient's home has also been achieved. Within the OCTRF/OCI system, the OCI/PMH has achieved the distinction of excellence. The hospital not only has provided multidisciplinary, quality care services to many Ontario residents over the years, it has also been the training site for about one-half of the Canadian-trained radiation oncologists in practice today in Canada. The research laboratories of the OCI have established an international reputation of considerable weight for their contributions to cancer treatment and research. The OCTRF centres have grown since their inception and now provide medical oncology as well as radiation oncology services. They also contribute to research and education, in addition to fulfilling their previous treatment roles.

The cancer system has worked closely with the general hospitals, particularly the host hospitals to which each regional cancer centre is attached. It has evolved outreach programs and collaborative interhospital programs. It has shared the funding of cancer research and education with other agencies, such as the National Cancer Institute of Canada, the Medical Research Council of Canada, and the Canadian Cancer Society Ontario Division. It has also received funding from other sources, such as the National Institute of Health in the USA. And, the system has evolved close relationships with the faculties of medicine and the university health sciences complexes.

These accomplishments have been achieved in a competitive environment, in a fiscally responsible way and with a minimum of government intervention.

Current Problems: A Crisis in the Making

Past accomplishments, however, are insufficient to guarantee current or future success. The abilities of the OCTRF/OCI to fulfill its mandate are compromised. The resources available to the cancer system represented by the two organizations are inadequate in quantity and quality to meet current, let alone, future needs. The system is stressed and demoralized by decisions that limit its ability to set priorities and that appear to distort priorities that are known to be urgent. The external environment is increasingly competitive in a fragmenting, destructive way to the cancer system. Many hospitals and their communities seek to develop cancer programs that are autonomous, not subject to the controls on quality and effectiveness the OCTRF/OCI centres require of themselves. Much larger hospital and health-care organizations in Ontario have developed co-ordinated efforts to attract the attention of the provincial government to their own goals and resource needs. These efforts appear to be more successful than corresponding efforts by the cancer system. They suggest limited attention is given by the Province to cancer control, affecting the ability of the OCTRF/OCI to present a coherent, effective provincial program. They also suggest the case for cancer control has not been made sufficiently strong.

The pervasiveness of cancer in the population and the past successes of the OCTRF/OCI stand in contrast to the resources allocated to cancer control. The cancer system represented by these two organizations received $84 million in 1983/84 (and expanded $87 million), about 84% of the total funding coming through the Ontario Ministry of Health. This provincial total is about the same as the budget of some hospitals and about one-half of the budget of one Toronto teaching hospital. Direct cancer research funding in 1984/85 from the Province was approximately 40 cents per Ontario resident. When supplemented by grants from other agencies (National Cancer Institute of Canada, Medical Research Council of Canada, various corporations, and the National Institutes of Health in the USA), the level remains under $1.00 per person; and, with education included, less than $1.40. In view of these modest levels of expenditure, further cutbacks in the real level of government spending on health care generally would have a comparatively greater impact on the cancer system than on the health system as a whole.

Facilities and equipment in the system are in need of immediate attention. Existing space in the PMH and in many of the regional cancer centres is inadequate and needs redevelopment. Highly technical equipment that is overworked and technologically outdated needs to be replaced. (A number of radiotherapy and diagnostic units are 20-30 years old.) Technological and other constraints require the equipment to go into new space. To correct inadequacies will cost as much as the total 1984/85 OCTRF/OCI budget for the required building programs alone, and about one-half as much, in addition, for the necessary therapy and diagnostic equipment.

The capital development needs are critical. The PMH was recommended for redevelopment in the previous provincial role study in 1972. Although the Ontario Ministry of Health approved the report, program funding has been withheld. Without funding to proceed, the 13 years that have passed since the recommendation have witnessed further physical deterioration and increasingly unacceptable overcrowding as workloads have climed. About $55 million will be required to redevelop existing facilities and to add 261,000 square feet of necessary space. A further $24 million, at least, will be required for equipment.

The OCTRF regional cancer centres also have urgent needs. The Toronto-Bayview Centre requires additional new radiotherapy machines to be able to assist the PMH to serve Metro Toronto patients who currently are waiting up to four weeks for treatment at the PMH because of overworked equipment and staff. This interim project will cost about $1.4 million for facilities, and an additional $2.8 million for equipment. Thunder Bay and Windsor need linear accelerators to ensure basic abilities to provide treatment. In 1988 the London Centre will lose its host hospital which will move to a new site. It has no choice but to start capital development; about $15 million will be required for facilities, and an additional $4 million for equipment. The Hamilton Centre has grown significantly in its service volume, research and education efforts, yet has had no major expansion since 1965 (apart from the introduction of a treatment room for a new accelerator). The Centre is inadequate in terms of the amount and quality of space it has for its current and future workload; an addition of 60-80,000 square feet is required; about $12 million will be required for facilities, and $4.5 million in addition for equipment. Depending on development options, these and other needs for the OCTRF centres will cost upwards of $45 million, and about one-half as much again for equipment, over the next decade.

Fiscal pressures are affecting operations as well. Programs requiring development and expansion have been deferred. Approved positions have remained unfilled due to restricted operating funds and inadequate equipment. Operating deficits, a condition avoided in the past, have become a reality. Waiting lists of patients requiring radiotherapy are up for four weeks long, particularly in Metro Toronto, and urgent cases frequently cannot be treated within the four-day standard which has been set by the PMH.

In the context of the provincial mandate given to the OCTRF/OCI and in the face of these needs, government decisions not to approve development at the OCI since 1972, and to build a new centre in Sudbury (whose operating and capital costs are not included in this study) appear problematic. The potential is high for distorting priorities, fragmenting services and for diminishing the effectiveness of provincial cancer control. For example, large teaching hospitals, particularly in Metro Toronto, are expressing strong interest in further developing their own cancer programs. Expensive, highly toxic antineoplastic agents are being provided anywhere a physician prescribes them. The need is pressing for a single organizational presence in cancer control that offers excellence in programming, provides leadership in treatment and care by example rather than by dictum, sets provincial goals and priorities, and is accountable to the government.

The study team was warned by its international advisors to avoid fragmentation. The U.S. experience, in particular, was cited as an example of a fragmented approach that typically provides less effective and more costly cancer control than in Ontario. The need to avoid multiple competitive centres, as in a number of U.S. cities and elsewhere, e.g., London, England, cannot be overstated.

The resource and organizational needs of the OCTRF/OCI are urgent. They stand apart from needs for any additional operating funds required to achieve a number of other important objectives: To enhance organizational effectiveness; to respond to rapidly changing technologies; to treat increased volumes of patients; to ensure a multidisciplinary mode of practice; and to enhance research and education efforts, despite resource pressures affecting the delivery of treatment and care.

Conclusions

After an 18-month assessment of the cancer system in Ontario, we have come to the conslusion that the bright contributions of the past by the OCTRF/OCI to cancer ways to help the regional cancer centres achieve as high a standard of excellence as circumstances and resources permit. Just as the regional cancer centre directors must accept the leading role of the OCI, so must the OCI accept the ambitions of the other centres to grow and develop. The proposed organization for cancer control in the Province must encourage these developments by protecting the unique qualities of the OCI and facilitating the achievement of the ambitions of all components of the system.

The sequence in which our three major recommendations are presented is significant: The first priority is to correct the serious deficiencies in facilities and equipment that have built up over the years and to provide the financial resources urgently required to meet the real needs of the next decade. Only after this has been initiated should attention be focussed on program changes and reorganization. In particular, the temptation to address organizational issues first in the hope that they will somehow alleviate financial pressures must be avoided.

Comments on the Detailed Report

The detailed report elaborates the essential accomplishments and problems of the current cancer system and its future needs. It recommends a wide range of responses control for the people of Ontario are about to diminish rapidly and may disappear altogether. A major infusion of funding is necessary to maintain, redevelop, and acquire new resources. These will be required to respond to increasing numbers of cancer patients and changing patterns of care. Organizational consolidation of the system will help to stabilize it an to extend its influence over cancer treatment and care throughout the health care sytem at large. This will help serve the aim of assuring patients they have access to equal quality of care wherever they may be initially diagnosed and assessed.

Recent advances in biotechnology and new methods in radiotherapy and surgery hold great promise for better cancer detection, prevention, diagnosis and treatment. The possibilities open to the Pronvice are exciting. We believe the investments and organizational changes proposed in this report will contribute to better cancer control for the residents of Ontario. They will also help to keep Ontario nurses, physicians, scientists, and other oncologic staff at the forefront of cancer control in Canada and internationally.

Major Recommmendations

To achieve the ends outlined above requires an implementation strategy which ensures that immediate deficiencies are corrected before a commitment to long-term goals is made.

Consequently our primary recommendations are to:

1. Correct current deficiencies by a major infusion of new money. Rectify the serious deficiencies in space and equipment at the OCI/PMH which have been neglected for more than a decade and have reached critical proportions. Proceed with recommended capital development for the OCTRF.
2. Develop a fully comprehensive cancer control program across the Province. This implies, in particular, the development of appropriate prevention and early diagnosis programs. It also implies the establishment of means to quickly utilize findings from current research which are likely to have an impact on prevention, early diagnosis and treatment.
   Such a program should include:
   - The continued development of the state-of-the-art of medical oncology, reinforcing co-ordination and interagency liaison on matters of practice between cancer centre and PMH physicians and those treating cancer patients elsewhere.
   - The continued development of the state of the art of radiation therapy across the Province (the gain from radiation therapy can be significantly improved through the increased accuracy achieved by simulation techniques, high-energy machines and careful treatment planning).
   - The support and development of oncology in the surgical disciplines.
   - Increased support for laboratory science and oncologic pathology to make use of improved knowledge in the biology of cancer and forthcoming techniques in tissue diagnosis and autopsy studies to enhance medical

audit, to define the action of drugs, and to improve the effectiveness of treatment.

- System-wide implementation and further development of the multidisciplinary approach to care to include nurses, pathologists and laboratory physicians, surgical oncologists and other oncologic workers, as appropriate, as equal members of the treatment team.
- Extensive, protected support for research and education.
- A commitment to psychosocial care as an integral, funded part of cancer treatment.
- Support and strengthening of dental oncology and pediatric oncology programs in the Province.
- Resources to co-ordinate oncology through the various regions of the Province and with the health sciences complexes so that standards of care can be comparable and evaluated wherever the patient is diagnosed and assessment is initiated.

3. Establish a unified cancer registry. To achieve the above changes and increased levels of development, we believe Ontario would be best served by the OCTRF and OCI merging into one, unified organization under a single Board. The new organization should preserve the existing regional basis of cancer control delivery. It should be given the mandate to co-ordinate all cancer control programming throughout the health care system in the Province, respecting the jurisdictional rights and obligations of existing hospitals, universities and other agencies with special interest in cancer control. It should also reaffirm the existing mandate currently held by the OCTRF/OCI to deliver programs through existing regional cancer centres and the OCI.

   This report recommends a mission and corporate structure for a new provincial cancer control organization. The proposed structure has organizational elements with responsibilities for regional cancer control programming in Metro Toronto and in regions covering the rest of the Province.

   It also has elements responsible for research and education; for finance and administration; and an Office of the President that includes an Executive Vice-President, the President's Office having responsibility for executive leadership and direction of the whole organization. The President would be accountable to the Board for general management, including strategic and fiscal management, and for ensuring the quality of programs and standards.

The implementation of these recommendations envisages the regional cancer centres assuming a comprehensive role and striving to become centres of excellence in their own right in prevention, treatment, research and education. In so doing they should strive to attain the excellence that has characterized the OCI, the achievement of which will be facilitated by its presence within the Province. At the same time, the OCI with its greater resources must continue to play a leading role in the Province and beyond its borders by building on past accomplishments and by finding in the interests of effective provincial cancer control. The extensive detail of the report must not, however, obscure the sense of urgency we feel on the need to inject significant amounts of new funds into the system forthwith. The process to establish a unified new organization for cancer control, in particular, should begin only after action has been initiated on priority capital development needs for the OCTRF and the OCI.

EDUCATION

SUMMARY OF OCTRF EDUCATION ACTIVITIES

Education Implications of Provincial Role Study Recommendations

The Provincial Role Study of Cancer Services in Ontario, commissioned by the Ontario Cancer Treatment and Research Foundation and the Ontario Cancer Institute, contained many recommendations covering a broad spectrum of educational activities and involvement.

Continuance and expansion of our role in education were recommended: in professional education, both undergraduate and postgraduate: in public and patient education: and professional communications.

The study acknowledged and commended the trend toward a wider co-ordination of oncology programs within the faculties of medicine and between the universities and the OCTRF/OCI Centres, and made specific recommendations to reaffirm and further these efforts. Included in the recommendations were the following:

- Regarding the acute and chronic shortage of radiation oncologists in the Province, it was recommended that OCTRF/OCI establish a joint health economics and statistics facility: a major responsibility of which would be to develop a manpower planning system and to conduct relevant manpower studies.
- It stressed the need to integrate surgical oncology into the multidisciplinary team. It recommended education programs in the wider aspects of oncology for clinicians, particularly those in surgical specialties. These courses would be offered at all levels, from undergraduate to surgical training and beyond, and the trainees would have maximum exposure to interdisciplinary teams and the co-operative process.
- Further, it recommended that the OCTRF/OCI explore with the Ontario Ministry of Health, the possibility of establishing satellite-based video conferencing capability and a surgical oncology group to consult with physicians in remote areas of Ontario.
- It urged the joint development, with the Ontario Medical Association, of an extensive continuing medical education program.
- In order to ensure that oncology is presented early in the training of nurses, it recommended formal links to nursing education through formal affiliations between the OCTRF/OCI and university faculties of nursing, community colleges, and the associated teaching and host hospitals where nurses obtain clinical experience.
- It recommended that the role of medical physics in oncology be augmented through increased liaison with universities and expansion of current training programs in medical physics.

Undergraduate and Postgraduate Medical Education

In the near future, the Foundation hopes to reactivate its subcommittees on undergraduate and postgraduate medical education. This is a step towards a co-operative review with the universities to ensure maximum co-ordination in the delivery of oncology education to medical students in the Province. All hope this will have a positive effect upon entry of newly qualified physicians into the speciality of oncology and will foster increased contact between graduate physicians and the staffs of the regional cancer centres, so that they all appreciate and participate in multidisciplinary cancer care.

Ivan H. Smith Memorial Studentships

In 1985, in co-operation with the Canadian Cancer Society Ontario Division, the Foundation supported 19 studentships for periods of 4 to 12 weeks. The Ivan H. Smith Program introduces the future physicians of Ontario to the many rewarding aspects of a career in oncology through observing and participating in the activities at the regional cancer centres. These studentships also can be taken as electives. In 1985, all studentships were taken outside of the academic year except for one elective. Participating centres were: Hamilton, Kingston, London, Ottawa, Toronto-Bayview and the Princess Margaret Hospital.

The Harold E. Johns Fellowships in Medical Physics

In 1985, 12 studentships were awarded and these were taken in the following centres: Hamilton, Kingston, London, Ottawa, Thunder Bay, Toronto-Bayview and the Princess Margaret Hospital. This program, which is intended to stimulate the entry of medical physicists into oncology, is funded from a special cancer services improvement grant from the Canadian Cancer Society Ontario Division.

Mr. Michael Wood, recipient of a Harold E. Johns Graduate Fellowship in Medical Physics will complete his fourth and final year under the fellowship at the Ontario Cancer Institute in April 1986.

Continuing Professional Medical Education

The joint pilot project for the provision of a "phone-in" cancer information service is functioning according to expectations. This community service is based at the Hamilton Regional Cancer Centre and is supported jointly by the Foundation and the Canadian Cancer Society Ontario Division. After approximately one year, the project will be reviewed to assess its performance before recommendations are made concerning the program's continuance and possible expansion throughout the Province.

In 1985, active programs for continuing education were carried out in the regional cancer centres and at the Princess Margaret Hospital through clinic days, seminars, guest lectures and lectures in the community by staff members.

On November 22, 1985, Dr. William Powers, Chief Radiation Oncologist, Harper Hospital and Chairman, Department of Radiation Oncology, Wayne State

University, Detroit, delivered the MacLaren Memorial Lecture at Henderson General Hospital in Hamilton on the topic "Precision, Local Control, and Function in Cancer Care".

On August 26, 1985, Dr. F.G. Pearson delivered the Gordon Richards Memorial Lecture at the 4th World Conference on Lung Cancer, held in Toronto. Dr. Pearson's topic was "Lung Cancer: The Past Twenty-Five Years".

During the annual meeting of the Canadian Oncology Society on September 9-12, 1985, in Vancouver, Dr. David A. Boyes, Director, Cancer Control Agency of British Columbia, delivered the W.G. Cosbie Lecture. His subject was "The Cytology Program in British Columbia".

One Ontario Cancer Foundation Lecture was awarded in 1985. In October, Dr. S.J. Robbroy of the Department of Pathology, University of Medicine and Dentistry of New Jersey, spoke on diethylstilbestrol related tumors under the title "DES Influences in Pregnancy" at the annual meeting of the Ontario Association of Pathologists, held in London, Ontario.

The Third Eleanor Leder Fund Lectureship in Oncology was delivered on April 10, 1985, at the University of Toronto on the topic "Prospectives for Cancer Control". The lecturer was Dr. Philip Cole, Professor of Epidemiology, School of Public Health, University of Alabama, Birmingham.

The 1985 exchange visitor sponsored under the Joseph J. Schiffer Exchange Program was Dr. Nathan Trainin, Korda Professor of Cancer Research and Professor of Cell Biology, at the Weizmann Institute of Science, Rehovot, Israel. This program is sponsored jointly by Mount Sinai Hospital and the Foundation.

The Harold G. Vail Visiting Professorship Fund at the Ottawa Regional Cancer Centre supported a visit from Dr. S.M. Jackson, Clinical Professor and Head of Division of Radiation Oncology, Cancer Control Agency of British Columbia. At the Ottawa Centre on May 28, 1985, Dr. Jackson gave two lectures entitled "The B.C. Experience with the Selectron" and "Results of Interstitial Implants in Cancer of the Tongue".

Mary Lou Erochko

LUNG CANCER: THE PAST TWENTY-FIVE YEARS

GORDON RICHARDS MEMORIAL LECTURE 1985*

F.G. PEARSON, M.D.**, *Toronto, Ontario*

In 1952, the Ontario Cancer Treatment and Research Foundation established an annual lectureship in memory of Dr. Gordon Earle Richards, one of Canada's pioneer radiologists and radiotherapists, who was appointed Director of the Institute of Radiotherapy at Toronto General Hospital at a time when radium and high-voltage x-rays were just coming into common use for the treatment of malignant disease. He established an international reputation for his contributions to clinical radiotherapy, and subsequently was appointed Professor of Radiology at the University of Toronto. He was Managing Director of the Ontario Cancer Treatment and Research Foundation between 1945 and 1949. I wish to thank the Foundation for the privilege of presenting the 33rd Gordon Richards Memorial Lecture.

From the perspective of a thoracic surgeon, I have chosen to review those aspects of lung cancer which have intrigued and challenged me during the past 25 years. In July 1960, when I commenced my appointment as a thoracic surgeon at the Toronto General Hospital, cancer of the colon and rectum was still the most common visceral malignancy in adult men. Primary cancer of the lung in women was relatively uncommon. Staging and the determination of operability of that period will appear primitive to the thoracic surgical resident of 1985. For most patients, in 1960, preoperative evaluation consisted of a thorough history and physical examination, relatively few laboratory studies, posteroanterior and lateral chest films, a careful rigid bronchoscopy and an exploratory thoracotomy. The only commonly used technique of invasive staging for lymphatic spread was scalene-node biopsy. Asymptomatic hematogenous metastases were identified only infrequently.

Although we were beginning to take an interest in objective tests of cardiorespiratory function, this evaluation was limited in most centres to clinical acumen, history taking and physical examination. At the time, a simple "stair test" was used to assess pulmonary function: If the patient could climb one flight of stairs without stopping, one could take out a lobe; climb two flights, and one could take out the whole lung. The trend towards limited resection for lung cancer was just beginning, and in those years we did many more pneumonectomies with the attendant loss of respiratory function and higher operative mortality rates.

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*Presented as the keynote address at the Fourth World Conference on Lung Cancer, held in Toronto on August 26-30, 1985.

**Surgeon-in-Chief, Toronto General Hospital; and Professor of Surgery, University of Toronto.

The clinical application of pulmonary function tests was in its infancy and blood-gas analysis was only available in research laboratories. Although positive-pressure mechanical ventilators had been developed in Denmark during the polio epidemic of 1952, only a few centres had them in 1960. Intensive care units were primitive, and chest physiotherapy was largely unknown in North America, though it was well established in the United Kingdom.

As many as 40% of presumably operable lung cancer was found to be unresectable at thoracotomy. The operative mortality for resection ranged between 10% and 20% and, in our hospital during the decade preceding 1960, was as high as 14%. These observations will be familiar to physicians of my own generation. The past 25 years have seen significant improvements in the selection of patients for surgery, and great strides have been made in peri-operative care. I will focus on those changes to which thoracic surgeons made an active contribution with an emphasis on our experience in Toronto.

IMPROVEMENTS IN INVASIVE STAGING

At the end of my postoperative training, during a visit to the Karolinska Institute in Stockholm, I met Dr. Eric Carlens who recently had reported his experience with the innovative technique of mediastinoscopy, and he introduced me to the procedure and the instrumentation. In 1963, we reported on our initial experience with this technique and by that time were satisfied that, with experience, one could safely and regularly biopsy lymph nodes in the paratracheal and subcarinal areas. Furthermore, it became apparent that mediastinoscopy could identify metastatic tumor in superior mediastinal nodes which were not evident in plane chest films. Then we began to assess the role of this procedure in the determination of operability in patients with apparently favorable (resectable) lesions.

By 1965, three groups had reported experience with mediastinoscopy for the preoperative assessment of patients with presumably operable lung cancer. These observations -- one from Holland, one from Germany, and our own report from Toronto -- were remarkably consistent. Using the conventional preoprative work-up and imaging of that time, approximately one of every three patients with apparently operable tumors was found to have metastases in superior mediastinal nodes biopsied at mediastinoscopy.

By 1972, we could describe a much larger number of patients and could recommend criteria for the application of mediastinoscopy to the definition of operability for patients with lymphatic spread to superior mediastinal nodes: Operate on only those patients with ipsilateral involvement, non-small-cell tumors, and N2 disease which was presumed completely resectable. This represented approximately 20% of the "mediastinoscopy positive" cases. Few surgeons recommended resection for patients with known contralateral spread, or small cell-tumors with N2 extension. Nor did we have good evidence that patients with N2 disease, which could not be completely resected, would benefit from surgical treatment.

Since then, a number of refinements in the original Carlens technique of mediastinoscopy have improved the accuracy of this assessment.

Left Anterior Mediastinotomy

Three groups of superior mediastinal nodes are inaccessible at conventional mediastinoscopy: A chain of anterior mediastinal nodes which lies in front of the aortic arch along the course of the phrenic nerve, and may be the site of spread from primary tumors in the left upper lobe or left hilum. Nodes in the sub-aortic window cannot be biopsied, nor can the posterior subcarinal chain which lies in front of the esophagus, but below and behind the accessible anterior subcarinal group.

Anterior mediastinal and sub-aortic nodes may be palpated and biopsied using the left anterior mediastinotomy first described by Steele and Marable. They used a vertical left parasternal incision with resection of one or two costal cartilages which provided a relatively extensive exposure. We modified this technique, and employed a transverse second interspace incision without resection of costal cartilage. This provides a more limited access. In patients with left upper lobe or left hilar tumors, cervical mediastinoscopy is still done initially. The biopsy material from cervical mediastinoscopy is evaluated by frozen section and, if the examination is negative, a left anterior, second interspace mediastinotomy is done under the same anesthetic. The anterior mediastinal nodes are palpated and accessible nodes biopsied through the mediastinotomy incision using a conventional mediastinoscope. The sub-aortic space is best palpated using a bidigital approach: Fingers are placed in both cervical and parasternal incisions at the same time. Tumors in the left upper lobe or left hilum metastasize to the left anterior mediastinal chain in 10% to 15% of cases.

Mediastinopleuroscopy

It is also possible to extend the mediastinal exploration into either pleural space. In 1976, Deslauriers and Beaulieu of Quebec City described their technique of mediastinopleuroscopy – a diagnostic procedure for certain intrathoracic lesions. On the right side, the mediastinal pleura is palpated and visualized through the mediastinoscope. The pleura can then be breached with a finger or sucker tip and, if the pleural space is free, the mediastinoscope is introduced to explore the upper one-half of the hemithorax. It is more difficult to explore the left side but this can be done predictably and safely with sufficient experience. Dissection is carried between the origins of the common carotid and subclavian arteries, the pluera identified and opened, and the scope introduced through this channel.

In a small number of patients, mediastinopleuroscopy may be used to stage presumably operable lung cancer. On the left side, some nodes in the anterior mediastinal chain may be palpated and biopsied with this technique. In patients with an associated effusion, pleural metastases may be identified and biopsied. Mediastinopleuroscopy provides easy access for palpation and direct examination and biopsy of superior sulcus lesions. I would emphasize, however, that mediastinopleuroscopy is of primary value in providing a tissue diagnosis, and is used only infrequently for preoperative staging.

Extended Cervical Mediastinoscopy

In 1985, Ginsberg of Toronto added a further modification to cervical mediastinoscopy which he named extended cervical mediastinoscopy. This modification is an alternative to left anterior mediastinotomy for the inspection and biopsy of anterior mediastinal and subaortic nodes. Finger dissection can be used to develop a plane anterior to the transverse aortic arch between the left common carotid and innominate arteries. The mediastinoscope then can be directed into this anterior compartment for direct visualization and biopsy. This modification allows biopsy of the anterior mediastinal and subaortic chain without the need for a second incision, or for left anterior mediastinotomy.

At the present time, the combination of cervical mediastinoscopy and the selective addition of extended cervical mediastinoscopy, left anterior mediastinotomy and mediastinal pleuroscopy will identify metastases in superior mediastinal nodes in 95% of these N2 patients. Metastases in the inferior and posterior subcarinal compartments still remain inaccessible to any of these invasive staging techniques.

NON-INVASIVE STAGING FOR N2 DISEASE

Non-invasive methods for the detection of N2 disease in the superior mediastinum include plane chest films, mediastinal tomography, computerized axial tomography, magnetic resonance imaging and nuclear scanning with either Gallium 67-citrate, or Cobalt 57-neomycin. The effectiveness of these techniques remains controversial. In Toronto, we have had no experience with the nuclear scans, but have conducted two prospective studies with the other imaging techniques comparing these results with the findings at mediastinoscopy and subsequent thoracotomy.

Mediastinoscopy and Mediastinal Tomography

In 1967, when Dr. R.J. Ginsberg was the senior resident on the Thoracic Service at Toronto General Hospital, he organized a prospective study to compare the accuracy of mediastinal tomography and mediastinoscopy in defining N2 disease in patients with presumably operable primary lung cancer. Anteroposterior and lateral tomograms were obtained in 97 patients who subsequently were proved to have bronchogenic carcinoma. A uniform technique of tomography was used and the results reported by the same radiologist, who was unaware of the findings at either mediastinoscopy or subsequent thoracotomy. None of these patients had evidence of mediastinal involvement by other methods of preoperative assessment.

Tomography was considered positive if soft tissue enlargement in the node-bearing areas exceeded 1.5 cm. Of the 35 cases deemed positive by tomography, 10 had metastases in mediastinal nodes at mediastinoscopy. This is a "false postive" rate of 28%. In 62 patients, the tomograms were interpreted as negative. Metastases were identified at mediastinoscopy in 23 of the 62 "negative" cases, a false negative rate of 38%.

Thus, in 33 of the 97 patients in this study, the tomographic interpretation was incorrect. The findings recorded at mediastinoscopy modified our management plan in 20 of the 35 patients with N2 disease.

Mediastinoscopy, Computerized Axial Tomography and Magnetic Resonance Imaging

In 1984, our Toronto group initiated a prospective study to evaluate the accuracy of mediastinoscopy, computerized axial tomography and magnetic resonance imaging (MRI) in patients with presumably operable primary lung cancer. The MRI and CAT scans were done using uniform techniques under the supervision of a single, experienced physician at the Ontario Cancer Institute. Published evidence had suggested that CAT scans were more accurate than tomograms for the definition of mediastinal nodes. MRI is a more recent modality which has potentially distinct advantages over CAT scanning and tomography: There is no radiation exposure. Contrast studies are not required to identify vascular structures. The electron activity varies in different tissues, and theoretically it is possible that malignant tissue may be distinguishable by its differing image.

Sixty patients with proven lung cancer have had all three studies and were evaluable at the time of writing. Unfortunately, the accuracy of computerized tomography and of MRI was no greater than that obtained in our 1967 study using mediastinal tomography. False negative results were obtained in 15% of CAT scans, and in 20% of the MRI scans. False positive results were obtained in 14% of the CAT scans, and in 12% of the MRI scans. Furthermore, it was disappointing to find that MRI was no more able to distinguish between malignant and benign tissue in lymph nodes than was computerized tomography. To date, non-invasive imaging has not significantly modified our indications for a staging mediastinoscopy.

RESULTS OF RESECTION FOR N2 TUMORS

In 1982, we described a series of 141 consecutive N2 patients, all of whom had a mediastinoscopy and all of whom underwent thoracotomy for a non-small-cell cancer that had metastasized to mediastinal nodes. These patients were divided into two groups: Group I – 79 in whom the N2 status was determined at mediastinoscopy before thoracotomy; and Group II – 62, all of whom the N2 status was established only at subsequent thoracotomy.

When the mediastinoscopy was positive, 85% of the tumors were resectable, and 65% of these patients had had a potentially curative resection. If operative mortality, unresectable cases and incomplete resections are included, the absolute five-year survival was a disappointing 9%. For those patients with a "negative mediastinoscopy" in whom the N2 disease was identified at subsequent thoracotomy, 92% of tumors were resectable and in 40% the resection was complete and potentially curative. The overall five-year survival was 24%.

Seventy-six of the 141 N2 patients had a complete resection and had an overall five-year survival of 24%. The five-year survival for completely resected squamous cell tumors was 34% in the "mediastinoscopy negative" group, and 18% in the "mediastinoscopy positive" group. These survival data are similar to those Martini and his colleagues reported in 1983. In Martini's report, the overall five-year survival was 29% in 151 N2 patients in whom resection was complete and curative.

Resection clearly is indicated in some patients with N2 lesions. We are convinced, however, that mediastinoscopy can play an important role in excluding a significant number of patients with N2 disease that cannot be completely resected. Tumors should be resected in almost all cases, in which it is technically possible, and in which the N2 status is determined only at thoracotomy. Operation is recommended in those "mediastinoscopy positive" patients whose N2 lesions are of non-small-cell histology, are confined to the ipsilateral side, and when the findings at mediastinoscopy suggest that a complete and potentially curative resection is possible. An analysis of our management of 100 consecutive patients whose tumors were considered operable before mediastinoscopy illustrates the impact of mediastinoscopy on our selection of N2 cases for resection. In 30 of these 100 cases, positive nodes will be found at mediastinoscopy. Twenty-four of these N2 lesions will be considered inoperable for reasons we have defined previously. Six selected N2 cases will have a thoracotomy, five will be resectable and four of the five resections will be complete and potentially curative.

INDICATIONS FOR LIMITED AND EXTENDED RESECTION

During the past 25 years, we have pursued the search for better information in a number of areas of persistent controversy in the surgical management of lung cancer: The indications for limited resection, the selection of patients for extended resection, and the search for effective adjuvants to surgical therapy. It is frequently difficult or impossible, however, for a single centre or institution to obtain valid answers to some of these questions. For example, at Toronto General Hospital it took 15 years to accumulate 70 cases of lung cancer managed by sleeve lobectomy. We compared the results of these 70 sleeve resections with 70 cases seen during the same years, with tumors of similar stage and location, which were managed by pneumonectomy. We concluded that in uncompromised patients, where the choice of sleeve resection is elective rather than forced by impaired pulmonary function, there is no difference in either morbidity or mortality between sleeve resection and pneumonectomy. Although these conclusions were statistically valid, the number of cases was small and all of the data were collected retrospectively.

Dispute continues about the indications for limited resection and for extended resection. Our own practice is to limit the resection to the least procedure which will encompass all of the al resection and wedge resection are used electively in selected patients.

We continue to adopt an aggressive surgical approach to primary lesions of non-small cell type. If a complete resection appears possible, the resection may include chest wall and diaphragm, the lower roots of the brachial plexus in superior sulcus tumors, and margins of the left atrium. We have reviewed and published the results of our own experience with sleeve resection, chest wall resection with and without radiotherapy, superior sulcus tumors, and N2 disease. Validity of this information suffers because these reviews all were done retrospectively, and the small number of patients in each of the comparative groups precludes randomized, prospective evaluation.

PROSPECTIVE RANDOMIZED TRIALS

Canadian Trials

In 1973, the National Cancer Institute of Canada (NCIC) initiated a multicentre, randomized trial of immunotherapy using adjuvant oral BCG in resectable lung cancer, under the leadership of Dr. A.B. Miller and a group of thoracic surgeons at the University of Toronto. Centres participated from coast to coast in Canada and, within two years, 308 evaluable patients had been entered.

This group of patients represented all stages of resectable lung cancer and all the patients in the study now have been followed for five years or longer. The overall five-year survival was 40%. There was no survival benefit in the treatment arm.

The National Institutes of Health Lung Cancer Study Group

In 1977, the National Institutes of Health in the USA initiated support for randomized, prospective trials of adjuvant therapy in resectable lung cancer. Our Toronto group were selected as one of seven original participants and our involvement in these well-organized, multicentre trials has been exciting, and a refreshing contrast to the frustrations of some of the past reviews conducted in isolation.

The data collected by this Lung Cancer Study Group is as accurate as any in the world today. Rigid compliance to the American Joint Commission Staging is required for all cases entered. All pathology material is reviewed by a reference centre at the M.D. Anderson Hospital in Houston, Texas. Study data are forwarded to a central registry at the National Institutes of Health in Washington, and their organization provides expert statistical analysis. All patients are carefully staged intraoperatively and nodal metastases are recorded using the mapping classification described by Naruke of Japan. Since 1977, nine trials have evaluated a variety of adjuvant treatments for resectable lung cancer at various stages and of differing cell types. As of April 1985, patient accrual was complete in three of these nine trials and some results now have been reported.

The first study, a trial using adjuvant immunotherapy, was initiated in 1977; it was designed to repeat the protocol reported by McKneally using intrapleural BCG and Isoniazid as a postoperative adjuvant in patients with Stage I, resectable non-oat-cell tumors. McKneally has reported a statistically significant survival benefit in resected Stage I cases receiving intrapleural BCG when compared with a group of retrospective controls. Between July 1977 and October 1980, the Lung Cancer Study Group entered 423 evaluable patients and then terminated the accrual. Follow-up is complete until February 1985. The Lung Cancer Study Group reported their results in 1983. Survival in these Stage I patients was excellent, but no benefit whatsoever was observed in the treatment arm. Another protocol evaluating adjuvant radiotherapy in patients with Stages II and III squamous carcinoma was initiated in February 1977. As of February 1985, 243 evaluable patients had been entered. Postoperative radiation consisted of 5000 rads administered in 25 fractions over five weeks. Many of us were disappointed to find no survival benefit in the treatment arm. A significant reduction in local recurrence was seen in the radiated cases, but there was no significant difference in the overall incidence of tumor recurrence.

Accrual is complete in a further trial of adjuvant immunotherapy versus combination chemotherapy in patients with Stages II and III adenocarcinoma and large-cell carcinoma. Between October 1977 and May 1984, 141 patients were entered; follow-up is complete as of February 1985. Immunotherapy consisted of intrapleural BCG and oral levamisol. The chemotherapy arm was Cytoxan, Adriamycin and cis-platinum. Median survival has been prolonged by approximately seven and one-half months in the chemotherapy arm. This is the first reported study which shows a statistically significant benefit for combination chemotherapy used as an adjuvant in completely resected, non-oat-cell lung cancer.

Accrual has been completed in another trial of adjuvant therapy in patients with non-small-cell tumors who still had minimal residual disease after resection. Between October 1979 and February 1985, 164 patients were entered. This two-armed study contained no control; both arms received adjuvants. One group received postoperative irradiation and combination therapy with cyclophosphamide, Adriamycin and cis-platinum. The other group received only postoperative radiotherapy. As of February 1985, there appeared to be a small but statistically significant survival benefit. The median disease-free interval was prolonged by eight months in patients receiving both chemotherapy and irradiation. These last two trials did not show striking benefits of adjuvant chemotherapy but they are statistically significant and are the first trials which clearly document such benefits in resected non-small-cell lung cancer. In the overall evaluation, however, these benefits must be weighed against the toxicity of the chemotherapy and irradiation.

Ongoing trials include a natural history catalogue for resected cases of early Stage I non-oat-cell cancer. Survival is so favorable in these T1 N0 cases that currently available adjuvant therapy does not appear justified. Combination chemotherapy with cyclophosphamide, Adriamycin and cis-platinum is being evaluated in selected Stage I cases (T2 N0 and T1 N1 categories). To date, no benefit has been observed for time-to-recurrence or survival in the treatment arm. Limited resection is under evaluation in a group of early Stage I cases (T1 N0) in which the tumor's location permits either lobectomy or a limited resection by segmentectomy or wedge. A recent protocol evaluates the role of postoperative irradiation in resected cases of non-oat-cell cancer which require a concomitant chest wall resection.

The most useful information from these Lung Cancer Study Group trials has been documentation of the natural history and outcome in resectable lung cancer. This includes sites of recurrence, time to recurrence, survival data and prognostic factors by stage and by cell type:

1. Site of first proven recurrence held some surprises for the participants. In Stage I lesions, 39% of the first recurrences were local, and 28% of distant metastases first appeared in the brain.
2. Time to recurrence, or the recurrence-free interval was calculated. Of Stage II sqamous cancers, 55% were free of recurrence at three years compared with 13% for Stage II adenocarcinoma at large-cell carcinoma.
3. Actuarial five-year survival for resected squamous-cell carcinoma generally was good, but there were significant differences in the subsets of Stage I: T1 N0 – 85%, T1 N1 – 75%, and T2 N0 – 64%. Surprisingly, completely resected N2 squamous cancer had an actuarial five-year survival rate of 48%. By contrast, survival at certain stages of adenocarcinoma and large-cell carcinoma clearly is less favorable. T1 N1 lesions have a five-year survival of 46% and N2 lesions have only a 26% five-year survival.
4. The American Joint Commission Staging clearly is the most significant prognostic factor. Cell type also is a significant prognostic factor: Survival is less favorable in Stage II and Stage III adeno- and large-cell carcinoma than for squamous cancers. A preoperative weight loss of greater than 10% adversely affects survival and, surprisingly, a preoperative elevation of the neutrophil count was an unfavorable prognostic indicator.

Modern 30-day Operative Mortality

In order to assess modern mortality rates following resection for lung cancer, the Lung Cancer Study Group analyzed the 30-day operative mortality at participating institutions between the years 1979 through 1981. During these three years, 2220 resections for lung cancer were done in 12 institutions from the five contributiong Lung Cancer Study Group centres. There were 1508 lobectomies, 569 pneumonectomies and 143 lesser resections. The operative mortality was calculated for each type of resection, and for different age groups.

Overall operative mortality for the 2220 resections was 3.7%. The operative mortality for segmental or wedge resection was 1.4%, for lobectomy 2.9%, and for pneumonectomy 6.2%.

The mortality rates increased with age – from 1.3% in patients under 50 years to 8.1% in patients over 80 years. It was revealing, nevertheless, that 85 patients over 70 years of age underwent pneumonectomy with a surprisingly low operative mortality of 5.9%.

The co-operation achieved by the participants in these North American trials allowed the collection of these mortality data – a task clearly beyond any single institution or centre. Furthermore, the study indicated that these figures were realistic goals for institutions throughout the country. These operations were performed by 28 surgeons in 12 different North American hospitals, and no significant differences were noted in the results between institutions.

CONCLUSIONS

Although progress in the surgical management of lung cancer appears frustrating and painfully slow, some headway has been made during the past 25 years. In the University of Toronto experience, 25% of patients operated on in 1960 had unresectable tumors. Improvements in staging and patient selection have reduced this incidence of fruitless thoracotomy to a much more satisfactory 5%. Operative mortality has dropped from 10% to 3%, and the five-year survival in patients operated on has increased from 23% to 40%. These improved survival rates are not due to better surgery; surgical technique has not changed appreciably in 25 years. Almost all of this improvement can be attributed to better patient selection. The accuracy of staging has been greatly improved using both invasive and non-invasive techniques to identify both lymphatic and hematogenous metastases. Surgeons generally have opted for conservative resection: The least operation which will encompass all of the identifiable disease. Operations such as sleeve lobectomy, segmental resection and even wedge resection now are used electively, and no longer are reserved for patients with severely compromised respiratory function. We see far fewer of those unfortunate patients who may have survived their cancer, but suffer a major respiratory disability following pneumonectomy, which was in much wider use two or three decades ago. We have seen significant advances in peri-operative care.

Several major obstables remain to further progress in surgical management. Despite all present efforts, staging obviously remains crude. Only 40% of resected patients will survive five years, and most of the deaths are due to local recurrence or disseminated tumor. There are still no dramatic adjuvants for many patients with non-small-cell cancers. With the exception of a few isolated screening programs in high-risk groups, efforts at early detection have been ineffective.

References are available upon request from:

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THE CYTOLOGY PROGRAM IN BRITISH COLUMBIA

W. G. COSBIE LECTURE 1985*

D.A. BOYES, M.D.**, *Vancouver, B.C.*

Carcinoma of the uterine cervix has never been the most common cancer among North American women but because it attacked younger women (than did breast or bowel cancer), and because these young women often had dependent families, gynecologists welcomed a technique -- the Pap smear -- that would help to prevent its development. We became interested in the late 1940s and, by 1949, a pilot project was underway. In today's world of controlled trials and sophisticated statistical evaluation, our early study design appears naive, nevertheless, we started a project and have continued it with some success. This paper describes our initial concepts (the late Dr. H.K. Fidler and myself), how these concepts were applied to a program, and summerizes the results of this program.

The initial pilot project in the Province of British Columbia obtained Pap smears from gynecologists' offices and outpatient clinics to determine whether the Papanicalou technique would work. In 1954, after it had become clear that cervical cytology did work, we undertook a study to determine whether the general application of this technique would reduce the incidence and mortality of invasive squamous carcinoma of the cervix.

Because we believed that a significant number of in situ carcinomas would advance to the invasive state if left untreated, we set out to answer the following questions:

Firstly: How could we determine if this were true? We decided: (a) to establish (as precisely as we could) the incidence of clinically invasive squamous carcinoma of the cervix in an in-house registry; (b) to determine the mortality from this disease for the population of British Columbia; and (c) to "generate" these rates in a uniform fashion for as long as it was necessary to show a negative or positive result. In conjunction with these ongoing determinations, we would remove as many in situ carcinomas as we could from our population.

Secondly: Who should be screened? We decided to screen the women in our population over the age of 20 and do this annually.

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*Abstract of a paper presented at the annual meeting of the Canadian Oncology Society, held in Vancouver, B.C., on September 9-12, 1985.

**Director, Cancer Control Agency of British Columbia.

Thirdly: Who should take the Pap smears? We decided that, because the general practitioners were in the front line of medicine in our province, they should be taught this technique, and that we should not introduce a full-scale program until we had shown the profession what was expected of them.

Fourthly: Who should study the smears? We decided that our best chance of detecting a significant difference would be to submit all the smears to a large central laboratory, which had consistent standards of reporting, and to strive for a quality control of a high standard.

The next question was: How should we investigate the suspicious or positive smear? Our decision (to do a cone biopsy of the suspicious or positive smear) was significant because this approach excluded the classic pattern of investigation, that is, diagnosing a lesion and then observing the subsequent outcome of the disease process. We chose cone biopsy for two reasons: First, we believed we could not measure the true extent of disease without it and, also concluded that a population-based program had to offer definitive treatment if it was to appeal to both patients and physicians. For the next 20 years Dr. Fidler and myself evaluated all of the resulting cone biopsies (later Dr. A. Worth joined us) because we wished to achieve consistency of reporting. From each cone biopsy we took 8 to 12 blocks in a radial fashion and did 10 serial sections through each block.

A final question concerned treatment. It was decided that the central laboratory would make recommendations with respect to treatment because gynecology was represented there. We made a further decision concerning endometrial carcinoma. Our pilot studies indicated that we could not pick up more than 50% of endometrial carcinomas with an Ayre's spatula and, because we believed that the spatula produced the best sample for the detection of cervical cancer, we told the medical profession in British Columbia that this technique was for this cancer only. The doctors were told that if the patient had abnormal bleeding, they must investigate by curettage or biopsy regardless of the outcome of the Pap smear.

With these decisions made public and with a highly co-operative medical profession, we began to train technicians to assess the smears and physicians to take them. By 1954, we were finding preclinical invasive carcinoma in our cone biopsies; arbitrarily, we gave names to two definitive phases of the preclinical invasion that were being identified in British Columbia women. We decided that if treatment was adequate the cone biopsy showed complete removal of an in situ cancer. If the lesion was incompletely removed, we advised "re-cone" (a second cone biopsy) or hysterectomy. If the cone specimen showed microscopic foci of invasion, we advised a hysterectomy and, if there was evidence of occult invasion, radical hysterectomy or radiation therapy. The support of the B.C. Medical Association and the UBC's Faculty of Medicine ensured virtually 100% compliance by the profession.

In the mid-fifties we established screening procedures in gynecological outpatient departments, venereal disease clinics and during physical examination for admission to our penal system.

To measure the results of the procedures we studied the accumulating incidence and mortality data. In the period 1955 to 1982, there was approximately a

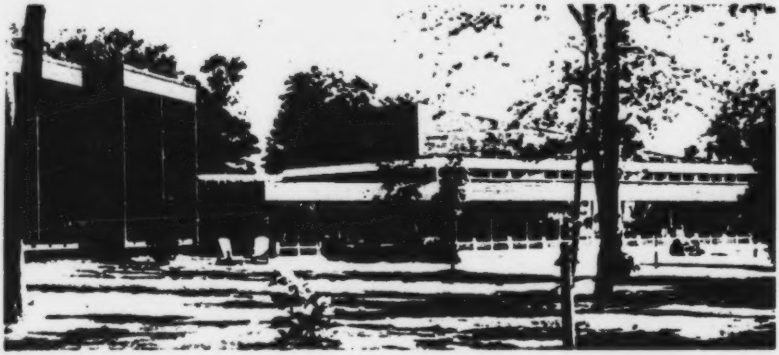
75% decrease in the incidence of invasive squamous carcinoma. This was achieved in spite of a rather rapid increase in preclinical carcinoma in young women in the latter part of the program. Similarly mortality due to cancer of the cervix has decreased by about 75%.

By the early 1970s, we concluded that the value of screening had been proven and, hence, decided to convert the program from a research project to a plan of treatment. We introduced colposcopy to simplify treatment. Because we were shifting the decision-making from a small group of experienced cytologist-gynecologist to the colposcopist, we kept this procedure off our fee schedule, with the co-operation of the B.C. Medical Association. We have set up 18 colposcopy clinics throughout the province and have trained gynecologists from our centre to run them on a sessional fee basis. The central laboratory refers patients to these clinics, which are sited throughout our province in relation to the centres of population. The data from the clinics is put into our automated record system so that we can maintain quality control.

In conclusion, the "Pap smear" program has been good for the women of the Province of British Columbia. It has produced a significant drop in mortality from carcinoma of the cervix. Fortunately the program was introduced at a time when it was philosophically acceptable. Today such a simple study would be beset by critical epidemiologists demanding such elaborate controls that it probably would outstrip available funding.

We estimate that this program has saved the lives of approximately 1136 young women of our society. We (and they) are most fortunate that Papanicolaou -- the originator of the examination -- had the vision to suggest to us the potential value of this test.

10TH CLINICAL CANCER RESEARCH CONFERENCE*



Geneva Park — Site of the
10th Clinical Cancer Research Conference

The theme of this year's conference was "Assessment of Response to Cancer Treatment". It was stimulated by apparent inconsistencies in the literature, where similar groups of patients receiving similar types of therapy appear to have quite different outcomes. The conference was divided into three major sections which considered: (i) techniques for evaluating tumor response; (ii) the implications of different endpoints, as well as sources of error and need for quality control; and (iii) quality of life, rather than shrinkage of the tumor, as a more important and global endpoint of response.

In the opening session Drs. P.Y. Poon (OCI) and J. Skilling (London Regional Cancer Centre) compared the relative potential of magnetic resonance imaging and CT scanning in the evaluation of tumor response. Magnetic resonance imaging is still evolving, but probably this technique will be superior for assessment of response in the central nervous system (CNS), but not in the abdomen and pelvis. Dr. W.M. Hryniuk (Hamilton Regional Cancer Centre) described problems associated with assessing the response to treatment of metastases in bone and showed that fine-section CT scanning could give much greater resolution than conventional x-rays or bone scans. This technique might allow more precise measurement of response to treatment in patients who so far have been regarded as having only "evaluable" and not "measurable" disease. Dr. I. Boxen (Hamilton Henderson General Hospital) described the current use of monoclonal antibodies in imaging; because of limited availability, their chief use is by local injection and lymphoscintigraphy. His data on melanoma suggest that monoclonal antibodies are not yet sufficiently reliable for the detection of metastases in lymph nodes.

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*Held at Geneva Park, Lake Couchiching, Ontario, September 30 to October 2, 1985.

Dr. D. Warr (OCI), described a study that estimated errors of measurement by asking several physicians to measure both simulated lesions and lesions in patients. These inherent errors are among the causes of variation in reported rates of partial response, particularly in clinical practice when one employs lax criteria of tumor response. Errors in patient assessment emphasize the need for quality control, and Dr. E. Eisenhower, from the NCIC Clinical Trials Group in Kingston. described the measures that this co-operative group has instituted in order to assess quality control. The follow-up of inconsistencies in data reported to the central office led to the detection of a number of patients in whom incorrect assessments of response subsequently were corrected. Now, this monitoring is supplemented by a visit every three years to participating institutions, during which random charts are checked and evaluated. Quality control measures should improve the reproducibility of clinical trials. Dr. T. Keane (OCI) discussed the value of tumor shrinkage as a predictor of response in radiotherapy. Although there is a correlation between tumor response at the end of treatment, or at a short interval thereafter, with eventual tumor cure, this correlation is far from absolute. There are many instances where tumors regress slowly after treatment but where eventually local control is achieved. In this situation, it is a major problem to determine when further intervention should be undertaken, such as surgery, in a patient who still has residual tumor after irradiation.

One of the guest speakers, Dr. A. Fuks, from the McGill Cancer Centre in Montreal, discussed the role of markers in assessment of tumor response. Although some markers, such as paraproteins in myeloma and HCG and alpha-fetoprotein in testicular cancer have been very useful, the weak sensitivity and specificity of most of the other markers, e.g. CEA, allows them to contribute very little to the clinical decision-making process. It is expected that current developments in molecular biology may provide new types of marker in the future.

The OCTRF Research Lecture was delivered by Dr. Charles Moertel, from the Mayo Clinic in Rochester, Minnesota, on the topic of "Problems in the Assessment of Tumor Response and the Reporting of Clinical Trials". Dr. Moertel emphasized the problems associated with drawing conclusions from trials that do not include a randomized concurrent control group. There are numerous instances where a historically controlled trial has given a quite different result from a concurrently controlled trial. He also pointed out problems associated with errors of measurement, and with the analysis of survival for patients who apprantly do, and do not, respond. The analysis of multiple subgroups within clinical trials and frequent analysis during the course of clinical trials also may lead to large errors in the results. Likewise, the summing of individual trials to produce an apparently significant result where none of the individual trials alone is significant may cause problems because one does not have good information about quality control in individual trials. His presentation was followed by a lively panel discussion centering on the interpretation of clinical trials in cancer therapy.

The second morning of the conference heard presentations by Drs. N. Boyd (OCI) and H. Schipper, of the Manitoba Cancer Treatment and Research Founda-

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Dr. J.W. Meakin, Mr. G.M. Adams, Dr. W.A. Wilkinson, Mr. M.A. Meighen, Mrs. J.P. Morawetz, Dr. G.R. Walker and Mr. R.D. Gray.

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Drs. P.J. Froud, J.F. Kotalik, R. Corringham, G.E. Catton, W.M. Hryniuk, G.C.K, Mok and R.D.T. Jenkin.

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Panel Discussants
Drs. N.F. Boyd, P. McGuire, M. Levine, H. Schipper and D. Osoba.

tion, who described different methods for assessing the quality of life of patients, during or after treatment. Dr. Boyd described the use of linear analog self-assessment scales and discussed methods by which the validity of these scales could be established. Dr. Schipper described a questionnaire known as the "Functional Living Index for Cancer". Dr. M. Levine (Hamilton Regional Cancer Centre) indicated methods whereby different quality of life methods could be compared through measurement of their signal-to-noise ratio. Dr. P. McGuire, from the University of Manchester, England, described his research into detection of major psychological problems being encountered by patients under treatment for cancer. A high proportion of patients are severely depressed, and also have sexual problems, that rarely are recognized by untrained personnel. Many of the symptoms are sufficiently severe to require psychiatric evaluation and treatment. He emphasized that, at present, the psychological effects of treatment are grossly underemphasized and described how nursing staff in a busy surgical unit in Manchester were trained to detect important psychological problems so that treatment could be undertaken. This session on quality of life was followed by a panel discussion. All emphasized that improved quantity and quality of patient survival were the most important goals of cancer therapy.

I.F. Tannock, M.D.
Chairman of Conference

CURRENT AND FUTURE ROLES OF MARKERS IN ASSESSMENT OF TUMOR RESPONSE*

A. FUKS, M.D.**, *Montreal, P.Q.*

The investigations of CEA as a tumor marker followed two parallel lines: Demonstrating that CEA was more than a serologic phenomenon by purifying the antigen, showing it to be a 200,000 dalton glycoprotein, deriving information on its amino acid and sugar composition; and second, testing human sera for antibodies to CEA. The latter was in keeping with the initial aims of the work, which were to investigate antigens responsible for eliciting immune responses to human tumors. Apparent anti-CEA reactions were demonstrated by hemagglutination in patients with early-stage gastrointestinal cancer and pregnant women; and the finding that such antibodies were absent in late-stage cancer led to the postulate that the antigen might be released into the circulation. The attempt to investigate this possibility led to the application of the relatively new radioimmunoassay (RIA) technology of the immunologic measurement of trace amounts of protein in the circulation. Not until later did we realize that such measurements of CEA could have practical import; this was not the prime reason for the experiment. Thus, the development of the RIA for CEA led to the demonstration of the antigen in the circulation of patients with gastrointestinal cancer and gave rise to the possibility of its clinical application. It was this demonstration, rather than an interest in the basic phenomenon of human tumor antigens that led to the explosion in this field. For example, between 1965 and 1969, the literature contains fewer than 30 citations of the original article whereas there are almost 50 citations in the two years following the appearance of the RIA paper. Finally, from 1975 to 1979, there are almost 500 citations of the original article and over 300 references to the assay methodology.

Clinical testing of the CEA assay and the development and marketing of a commercially available RIA for CEA allowed the widespread application of the method. The strict anti-tumor specificity demonstrable in the early work led many to expect that the RIA for CEA could be used as a screening test for malignancy (an editorial in the *British Medical Journal* was entitled "New Test for Cancer"). Thus, the demonstration in the early and mid-1970s that CEA positivity was not confined to patients with tumors of the gastrointestinal tract led to more detailed investigations of the application of the assay and to the many controversies that have characterized the field.

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A number of groups have demonstrated that sera from patients with breast and lung tumors, as well as those with gastrointestinal tract malignancies, were positive in the RIA. Secondly, patients with earlier stage disease were less likely to demonstrate positive reactions. Finally, sera from patients with nonmalignant inflammatory diseases, such as cirrhosis and ulcerative colitis, were positive in a small but reproducible proportion of cases. It became clear that, as in many other instances of the introduction of a new diagnostic or therapeutic technique, the general experience rarely fulfills the initial enthusiastic expectations. Nevertheless, the indications for CEA measurement established in 1978 are still valid today. These include: preoperative prediction of tumor stage, postoperative prognostication based on the pattern of CEA levels, and postoperative management of the potentially cured cancer patient, including second-look surgery and chemotherapeutic intervention.

Concurrent with the clinical analysis, a number of laboratories were pursuing three lines of immunochemical and biochemical investigation. The structure of CEA was being elucidated with respect to the composition of material derived from different tumors, N-terminal sequence analysis, effects of chemical and enzymatic manipulation on immunologic activity, and characterization of glycopeptides derived from the purified molecule. A second set of investigations concentrated on the identification of materials from normal and malignant tissues that were immunologically related to but structurally distinct from CEA. A series of 12 such materials, obtained from a variety of sources, became the subject of much attention, in part because these substances may represent "normal" counterparts of CEA or members of a large family of related molecules with variable cellular expression. Furthermore, it was postulated that such cross-reactive materials might be detected by the radioimmunoassays for CEA and hence represent a source of false positive reactions. Finally, a variety of different assays for CEA were devised, differing in separation techniques, sample extraction, and source of anti-CEA antiserum. This specificity of the antiserum employed in the clinical assay became a central issue, because it was thought that some of the relative lack of specificity (false positives) could be attributed to antisera with multispecific reactivity. However, despite such manipulations of sera and techniques, the different assays show a high degree of concordance with respect to type of disease groups and stages that manifest positive reactions. It is likely, however, that this situation will change as monoclonal antibody reagents, the specificities of which can be rigorously selected and defined, begin to have an impact on immunological assay systems.

One interesting and useful byproduct of the work on anti-CEA antisera has been the use of radiolabelled antibodies in vivo for radionuclide scanning for occult tumor and for potential vectorial delivery of therapy. Such experiments have met with some success and are likely to gain wider use in the near future.

Most of the effort in the past decade has concentrated on defining the clinical role for measurement of serum CEA and its impact on diagnosis and therapy. One must, however, recall that the initial questions that led to the description of CEA revolved around the basic nature of human malignancy. Although a large research effort has been devoted to determining the structure of the molecule and its relatives, relatively little is known about the biologic role of CEA both with respect to embryogenesis and malignant transformation. This is in part a reflection of the desire of biomedical research to promote the applications of basic discoveries and perhaps, in larger part, a lack of viable experimental models in which to test hypotheses. There is no clear-cut animal model that presents a CEA-analogue, and in vitro investigations on human cell lines have been limited to cellular localization of the molecule and analysis of its secretion. This situation may change in the future as newer analytic methodologies are brought to bear on the problem. It is likely that the clinical utility of CEA will increase both from a refinement of immunologic methods of detection as well as from a more detailed understanding of the basic biologic nature of this interesting molecule.

References are available upon request from:

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CURRENT STATUS OF MONOCLONAL ANTIBODIES IN IMAGING AND TREATMENT OF CANCER*

I. BOXEN, M.D.**, *Hamilton, Ontario*

Koehler and Milstein discovered the technique for producing monoclonal antibodies (MoAbs) in 1975. This yielded clinically useful quantities of chemically identical antibodies, and their very high antigen specificity led to the improvement of laboratory assays, to much research and, even now, to therapy for some diseases.

Because of their very high specificity, MoAbs have been promoted as a means of detecting and treating cancer. By selecting those MoAbs that bind to tumor cells but not to normal cells, we have MoAbs specific for what are called "tumor-associated antigens". These MoAbs, when labelled with an imaging agent such as a radionuclide, allow visualization of the tumor. Treatment is also feasible if one uses radionuclides that cause high radiation damage. It has also been proposed that toxins be attached to the MoAbs. In a few select cases, treatment with just the antibody may be possible via activation of the complement system or killer T-cells.

Unfortunately, the highly specific MoAbs have some of the side effects encountered when polyclonal antibodies were used to detect and kill cancer cells. Not all the cancer cells in an individual express the specific antigen to which a chosen MoAb is directed. This heterogeneity in tumor-specific antigen expression changes also with time. Cross-reactivity of MoAbs with normal tissue can be minimized or even eliminated by appropriate selection but there is still non-specific localization due to normal distribution throughout the body, metabolism and elimination. The MoAb may remain on a tumor cell for only a few minutes due to shedding of antigen-antibody complex or internalization and degradation followed by exocytosis. As a result, tumor detection by radiolabelled MoAbs is not yet sensitive enough to supplant other methods, and tumor therapy by radiolabelled MoAbs is severely limited both by failure of adequate tumor uptake and by radiation damage to normal tissue.

The distribution of MoAbs and tumor uptake can be improved by the use of instead of whole antibodies for their specific binding fragments F_{ab} and $F_{(ab')_2}$. The smaller fragments penetrate body compartments and solid tumor better than the whole antibody and are partially eliminated by the kidneys, thus reducing the background. Recently it has been shown that uptake in certain tumors increases following radiation or hyperthermia, due to increase in non-specific capillary "leakiness" in tumors with extensive neovascularization. Fragments also elicit less of an immune response than whole antibodies.

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In some cases, the tumor-associated antigen is expressed not only on the cell surface, but also is shed into the bloodstream in high quantities, interfering to a certain extent with tumor uptake of MoAbs. Recent work has shown that if the bloodstream is cleared of these antigens with excess unlabelled MoAbs, the tumor cells will take up more radiolabelled MoAbs thus improving the effectiveness of radiotherapy.

Antigen-antibody complex formation in plasma has not been a significant clinical problem. Sensitivity for detection has been increased by injecting MoAb against the radiolabelled MoAb (used for imaging) to clear background to improve lesion-background ratio. Unfortunately, such a plasmaphoresis technique has not worked in patients who have a significant immune response to previously used MoAb.

The choice of route of administration of MoAbs may also affect localization. In malignant melanoma that has spread to local draining lymph nodes, a subcutaneous injection near the site of the primary should maximize uptake in the involved nodes. To date we have had limited success in our research into the application of this technique for detection of tumor. If this method can be made to work, we should be able to treat malignancy with radiolabelled antibody given via lymph-channel cannulization and injection.

At present, imaging with MoAb relies mainly on the radionuclides ^{131}I and ^{111}In, the ^{131}I ionically bound to the antibody and the ^{111}In via a covalent labelling with DTPA (diethylene triamine pentacetic acid). The ^{131}I is also used for therapy because of its beta-emissions. Higher-energy beta emissions are available with ^{90}Y. Currently, this radionuclide is used for panus lysis in large joints, such as knees, but is being investigated for use with MoAbs. Short-ranged alpha particles produce more selective cellular damage. The alpha emitters ^{212}Bi and ^{211}At also are being investigated for possible clinical use.

Except for a few isolated cases, radiotherapy with MoAbs probably will not deliver enough radiation to kill tumors without causing significant damage to such tissue as bone marrow, intestines, and liver. It therefore will rarely be the sole means of treatment. However, such treatment may be an important adjunct to local teloradiotherapy where it would maximize tumor radiation dose.

Before considering MoAbs for either cancer detection or therapy, one must choose the specific MoAb. This choice will require histological diagnosis and probably a biopsy specimen. Heterogeneity of tumor-associated antigen expression on cell surfaces probably will require one to use a "cocktail" of different MoAbs. If so, the net benefit of MoAbs over polyclonal antibodies will be their ability to reduce or eliminate crossreaction with normal tissue.

Because of these problems, the initial enthusiasm over MoAbs with respect to cancer detection and therapy has been greatly tempered. Hence, it may be some time before MoAbs find a place in the routine clinical management of cancer patients.

MEASUREMENT ERROR AND CRITERIA FOR TUMOR RESPONSE*

D. WARR, M.D.**, *Toronto, Ontario*

In reports of chemotherapy trials, the result displayed most prominently is the frequency of complete plus partial responses. However this figure is highly variable. For example, the response rates for carcinoma of the colon treated with 5-FU range from 8% to 85%. Usually this variation is attributed to differences in patient characteristics, different schedules of drug administration, disagreement over what constitutes an evaluable patient, or problems with small numbers, i.e., a sampling error. However, both clinical and experimental evidence shows that these explanations are insufficient.

Davis et al used the results of the Clinical Oncology Group (COG) chemotherapy trial for metastatic breast cancer to illustrate how response rates may be affected by differences in evaluation criteria. When a single data set was re-analyzed according to the COG, Eastern Co-operative Oncology Group, Southwest Oncology Group, or Southeastern Cancer Group assessment criteria, the response rates for evaluable patients ranged from 38% to 52%. Similar changes in results after altering the response criteria have been reported in chemotherapy trials for prostatic cancer and malignant melanoma.

In 1976, Moertel and Hanley described a study on measurement error which used simulated tumor nodules (STN). They concluded that the category of minimal response was unreliable and that even a conventional definition for partial response (PR) would lead to a 5% to 10% response rate due to error alone. Intrigued by these results, we carried out a similar study but also used clinically relevant lesions -- lymphadenopathy, hepatomegaly, metastases on chest roentgenograms -- and examined the effect of altering response criteria.

As examiners, our study used eight physicians -- four medical oncologists and four medical oncology residents. The STN were 16 spheres ranging in diameter from 1.9 to 6.5 cm that were placed in random order on a foam rubber mattress and covered by another thin (1.3 cm) layer of foam rubber to simulate skinfold thickness. The examiners were given 17 chest roentgenograms (posteroanterior view) showing a total of 37 clearly defined metastases. Fourteen patients with head and neck cancer or lymphoma associated with enlarged neck nodes volunteered for assessment. Fifteen patients with hepatic enlargement due to metastatic cancer also agreed to participate.

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The maximum and perpendicular maximum diameters of the lesions (excluding those in the liver) were recorded by each physician and then multiplied to give an estimate of cross-sectional area. For the liver, the span below the right costal margin was added to the span below the xiphisternum to give a single linear measurement. To calculate the false response rates due to measurement error, we then compared all possible pairs of areas estimates for a single lesion. A false PR was defined as an apparent shrinkage of >50%. A false minimal response was defined as an apparent shrinkage of 25% to 50%. A false disease progression was defined as an increase >25%. The effect on false PR rate of measuring more than one lesion was simulated by comparing the sum of the estimates of cross-sectional area for two and for three specified lesions. By comparing triplets or quadruplets of measurements on a single lesion, it was possible to simulate the effect of requiring that two or three successive measurements must show at least a 50% reduction before declaring a PR.

A plot of lesion size versus the probability of false PR indicated that the error rates for the STN were clearly greater for smaller lesions. A similar variation was not apparent for the neck nodes. Thus, factors other than size were influencing the reliability of measurement of lymph nodes.

Similar to the findings of Moertel and Hanley, the false PR rates for the liver size, neck nodes, and smaller STN were approximately 10%. The results for the lung metastases were much better, presumably because these lesions were immobile and flat in contradistinction to the other tumors. Inclusion of minimal response as an indicator of antitumor activity increased the error rate substantially. Similar results were obtained for the category of false disease progression. To lower the error rates to a level identical to those for PR would require redefining disease progression as a >100% increase in area.

When two or three lesions were assessed (rather than a single index lesion), the false categorization frequency decreased. Changing the definition of PR to require that all lesions decrease in area by 50% rather than simply the sum of areas led to a further decline in false PR.

The underlying assumption in these results is that, with ineffective treatment, tumor size will not change between assessments. This assumption can be changed to allow for tumor growth. We derived a power curve from the lymph node data by comparing measurements on lesions of different size. It related the relative change in cross-sectional area to the probability of declaring that change to be a PR. A typical volume doubling time for carcinomas is three months, which would translate into an increase in cross-sectional area at one month (the usual time of reassessment) of only 17%. From the power curve there would still be approximately a 7% chance of declaring a false PR. Similar calculations have been carried out for more rapidly or more slowly growing lesions.

Our results with clinically relevant lesions were similar to those of Moertel and Hanley but still may not accurately portray those in clinical practice. All of the lesions had clearly palpable or visible margins – an uncommon finding in the typical chemotherapy patient. The examiners were aware of the study and this may have led to more careful measurements. We have also not taken into account physician bias; our desire to achieve tumor shrinkage may cause subsequent measurements to underestimate the true size. All of these considerations would tend to increase the false response rates which we have calculated.

For Phase III trials palliation and survival are the most relevant outcomes, yet the response rate is often regarded as the primary indicator of patient benefit. We believe that this practice will continue until more refined measures of palliation are developed. From this study and our own clinical experience we suggest criteria which will decrease the number of false responses and exclude short-lived shrinkage (which rarely translates into worthwhile symptomatic improvement). The definitions listed in Table I cannot substitute for more appropriate endpoints, but may allow a more realistic assessment of the potential for patient benefit.

References are available upon request from:

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TABLE I
Proposed Changes in Criteria for Tumor Response: Phase III Trials

CRITERIA	SUGGESTED CHANGES
Disease progression	Redefine as a 100% increase in area* of any measurable lesion, or the appearance of new lesions
Minimal response	Term should be abandoned
PR	Redefine as a 50% decrease in area* of all index lesions recorded at 2 consecutive assessments at least 1 mo apart; no new lesions should occur; require a minimum duration† of 3 mos; require index lesions to have an initial mean diameter of 2 cm
Complete remission	Require disappearance of all evidence of disease recorded at 2 consecutive assessments at least 1 mo apart; require a minimum duration† of 3 mos

*For malignant hepatomegaly replace "area" with sum of measurements of the liver edge below the costal margin in the midline and MCL. Distance of the liver edge below the costal margin in the midline or MCL must exceed 5 cm to use hepatic disease as a marker of response.

†Duration of response is the interval between start of treatment and last assessment at which response criteria are satisfied.

COMPARISON OF MR AND CT IN ASSESSMENT OF TUMOR RESPONSE*

P.Y. POON, M.B.,B.S.**, *Toronto, Ontario*

Both MR and CT can provide detail morphological information of tumor response. In comparing these two modalities, the following points are important:

Soft-tissue Contrast Resolution. The contrast of MR is provided by a number of parameters, i.e. T1, T2, relaxation times, proton density, and flow, whereas that of CT by one paremeter only, i.e. electron density.

Spatial Resolution. Currently the fourth generation CT scanner has a better spatial resolution than an MR imager operating at a low-magnetic-field strength (e.g. at 0.15 Tesla). However, with increased magnetic field strength (up to 1.5 Tesla), and application of surface coil, the two techniques soon will be equal.

Effect of Involuntary Movement. The image quality of MR suffers much more from cardiac and respiratory movements than CT. It is worth noting that MR of brain, spinal cord and pelvis is not affected by these involuntary movements.

Direct Multiplanner Imaging. MR can image directly in the transverse, sagittal and coronal planes. On the other hand, CT is quite limited in this respect. Sagittal MR images of the brainstem and spinal cord have been extremely useful in the diagnosis and follow-up of tumors in these areas.

Bone Artifacts. To visualize tumors in the posterior fossa, CT is often handicapped by bone artifacts. MR does not have this limitation.

Besides the morphological changes, do the T1 and T2 relaxation times of the tumor change during treatment. And if they do, what are the clinical implications?

Quite reliable quantitative measurements of T1 and T2 relaxation times can be obtained by special MR imaging pulse sequences. We have undertaken a pilot project to determine the variation of T1 and T2 relaxation times during treatment of relatively large solid tumor masses. A base line MR examination is done before treatment. Serial examinations are then obtained at regular intervals during and after therapy. The preliminary results are not impressive. The variation of T1 and T2 observed so far is minimal. However, patients will be followed further to see if we can identify a pattern of changes.

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TUMOR RESPONSE IN RADIOTHERAPY*

T.J. KEANE, M.B.,B.Ch.**, *Toronto, Ontario*

One's view of tumor response in radiotherapy depends on one's background and training. Radiobiologists tend to view tumor response in mechanistic terms while clinicians tend to view the subject in a more utilitarian manner because they hope to use the knowledge in clinical decision making. Our present conceptual knowledge of tumor response has allowed us to develop a number of models within which we can consider the various factors, which modify radiation response. The conceptual models of tumor response emphasize the fact that factors other than tumor cell kill may be important in determining responsiveness. In particular, we must consider the influence of cell-loss factors in relation to tumor doubling time. Experiments in animals show a wide range of relationships between radioresponsiveness and radiocurability. These experiments suggest a considerable variation in the ability of tumor response to predict ultimate radiocurability.

At the clinical level, tumor response is always gratifying although the relationship to ultimate radiocurability is also variable. Clinical studies mainly of squamous cell carcinomas has shown that responsiveness at the time of completion of radiation, and for periods up to three months following radiotherapy, do not totally predict radiocurability. However, this is not to say that radioresponsiveness is not important. A record of radioresponsiveness may be an important aspect in clinical decision making i.e. in deciding at what point a tumor, which has failed to respond, likely is incurable. For example, critical to management are the response patterns following radiotherapy for other non-squamous tumors, such as adenocarcinoma of the rectum and benign tumors such as juvenile angiofibromas. The failure to recognize the slow response of these tumors to radiotherapy may lead to premature initiation of secondary treatment.

Radiation oncologists have not used tumor response as an end-point in cancer management not because it provides inadequate information but simply because they usually have better end-points, i.e. local control and cure. While response is not used in the reporting of end-results, nevertheless it is important that clinicians recognize its validity if the conceptual modules being generated by the radiobiologists are to gain acceptance and application in day-to-day practice.

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MEASUREMENT OF THE CLINICAL STATUS OF PATIENTS WITH CANCER*

N.F. BOYD, M.B. B.S.**. *Toronto, Ontario*

The work described was done in collaboration with Drs. P. Selby, J. Etazedi-Amoli and J. Chapman, and with the assistance of H.Sutherland and S. Hogg.

Although many have recognized the need for a method of assessing the quality of life of patients undergoing therapy for cancer, no one has described an adequately evaluated or feasible method of making such an assessment. We describe a method in which 31 items are assessed by patient's self-report using linear analogue scales. Eighteen items that enquired about general health problems were derived from the Sickness Impact Profile -- an established method of assessing the effects of health upon behavior and function. Thirteen items, enquiring about major problems associated with breast cancer or its treatment, were derived from clinical experience and the opinions of patients with this disease.

Each item had been evaluated for its content, feasibility, reliability, and validity. The instrument appears easy to use, acceptable, and reliable. Validity was evaluated indirectly, because no standard method of measurements of quality of life exists for comparison. Most items appeared valid when compared to alternate measurement methods including the Sickness Impact Profile and evaluation by a physician in a structured interview. The correlations betwen items in the instrument were analyzed by factor analysis and seemed to fit with the clinical features of breast cancer. When the method was applied to patients with different disease characteristics, those with metastatic disease were clearly distinguished by their scores on items related to physical function, and patients receiving chemotherapy were distinguished by their scores on treatment-related toxicities. Within a limited context, the method was also able to detect change in scores with time.

This work illustrated possible approaches to the scientific evaluation of methods of measurement to be applied to the subjective components of patients' illnesses. The method assessed in this study appears suitable for some purposes, such as the general description of the clinical status of patients. However, further evaluation and development will be required before it is known whether this method has predictive value in identifying patients who are going to develop particular clinical difficulties, or whether it can be used to help decide between alternative treatments, for example, within the context of a randomized control trial.

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*Abstract of a paper presented at the 10th Clinical Cancer Research Conference held on September 30 to October 2, 1985, at Geneva Park, Lake Couchiching, Ontario.

**Medical Oncologist, Ontario Cancer Institute, Toronto.

THE FUNCTIONAL LIVING INDEX FOR CANCER*

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Functionally quality of life can be described as a composite of four dominant contributors: physical/occupational, psychological state, sociability, and somatic discomfort. The relative importance of each component to overall quality of life is as yet unclear. Even allowing for the influence that primary question selection has on overall weightings which emerge from the factor analysis process, a remarkable consistency can be observed in the ordering of component weights across most published studies. Thus, quality of life appears to be an underlying process which is amenable to measurement.

The modern era of quality of life studies began in 1976 when Priestman and Baum[1] proposed a 10-item quality of life questionnaire (for use in breast cancer patients whose sum score of 100 seemed to correlate with chemotherapy toxicity). In addition, when readministered at 3 months, the test seemed to be able to distinguish between those patients who had had an objective tumor response and those who had not. Later, Spitzer et al[2] took the process a step further and devised a five-question index to be administered by a physician or a nurse. Subsequent attempts began to emphasize patient self-administration and broader reliability and validity testing, employing multiple observer and population techniques. The Functional Living Index for Cancer (FLIC) was developed at the Manitoba Cancer Treatment and Research Foundation[3]. The 22-item questionnaire, designed for patient self-administration at frequent intervals, was given to 837 unselected patients representing the range of clinical practice, both inpatient and outpatient, encountered at two major Canadian cancer centres. Validation studies showed that it was sensitive enough to distinguish follow-up patients from those hospitalized and those hospitalized from those in palliative care units. Factor analyses on validation samples of 175, one from each co-operating institution, were remarkably stable, adding further to the weight of evidence that quality of life is a measurable and evaluable construct. Thus we have concluded that FLIC and subsequent measures may be used not only as global estimates of quality of life but also as screening tools in the identification of specific dysfunction.

Current studies employing the more cumbersome but ultimately essential longitudinal study approach are underway, frequently in conjunction with major clinical trials groups. In the process, measured quality of life is being incorporated into cancer clinical trials as an outcome measure.

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*Abstract of a paper presented at the 10th Clinical Cancer Research Conference, held on September 30 to October 2, 1985, at Geneva Park, Lake Couchiching, Ontario.

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When fully established, quality of life outcome measures will have a powerful influence on the clinical trials process.

First, we will have an outcome measure which measures the end product of the health care system insofar as the patient is concerned. This tool will provide insight and direction, useful in solving accrual and compliance problems, which currently retard many clinical trials. If, as some current data suggest, only 20% of eligible patients are entered in trials -- it is difficult if not impossible to generalize from our clinical trials research.

More specifically, the application of quality of life indices will have considerable influence on clinical research in palliative care and curative therapies. When it is not possible to offer a reasonable prospect for cure, longevity per se ought not be the sine qua non. Palliation by definition means preservation of quality of life. To a considerable extent the hospice movement has focused on pain; yet, clearly, somatic discomfort is only part of the total quality of life. The availability of quality of life measures will assist us to refocus toward broader goals. Thus anticancer and quality of life management ought not to be considered mutually exclusive alternatives, as is not often the case.

Where intensive therapies are being evaluated, the addition of quality of life assessment may explain apparent discrepancies between patient function and clinical response and pose some new questions for clinical trials investigators. For example, if, based on traditional criteria, two clinical trials provide similar outcomes, a significant discrepancy between quality of life outcomes would readily influence subsequent treatment selection. However, what do we do with divergent results, that is, where an outcome viewed inferior by classical criteria is associated with a significantly improved overall quality of life response? Which treatment arm does the investigator then recommend, the one with the greater response and/or survival or the one with quality of life outcome that appears superior? A valid measure of quality of life provides us with some alternatives: (a) it may be possible to alter therapy in the "traditionally" superior arm to improve the quality of life outcome; and (b) if the former is not possible, at least we are in the position to offer patients not only response, disease-free survival, overall survival, and medical toxicity information, but also quality of life information. This will assist the patient to make an informed decision.

To the extent we are unable to prevent disease, the ultimate goal of medicine is to effect a cure and return the patient to a life-style not diminished by the illness and its treatment. The scientific power of modern medicine provides the biologic rationale to intervene with a force never before possible. The rigorous development and application of quality of life assessment is neither unscientific nor in competition with basic medical science as we know it. It merely serves to emphasize that the proper study of mankind is man.

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COMPARISON OF METHODS FOR ASSESSMENT OF QUALITY OF LIFE IN PATIENTS RECEIVING CANCER THERAPY*

M.N. LEVINE, M.D.**, *Hamilton, Ontario*

This comparison of methods for the assessment of quality of life (QL) in patients receiving cancer therapy will focus on the comparison of QL instruments in the setting of a cancer clinical trial. The paper will make some general comments concerning QL, and describe our Stage II adjuvant breast study in which we are assessing QL; it will describe a method of distinguishing a good instrument; and review the assessment of QL in our Stage II breast cancer trial using various QL instruments.

Why measure quality of life? If we had therapies that could cure every patient with minimal side effects, there might be no need for QL assessment. However, we often are looking for small benefits as measured by slight improvements in survival or by evidence that we have arrested tumor growth. Often treatments are toxic and we are often so preoccupied with tumor response that we forget to ask how the patient feels. In cancer patients QL assessments can have two benefits: 1) they can lead to improved patient management; and 2) they can provide a useful outcome measure in clinical research.

A QL measure can be used for one of three purposes: Discrimination -- to distinguish between different QL states; Prediction -- as a prognostic indicator; and Evaluation -- to measure change over time. In a cancer clinical trial it is an evaluative instrument that is most important.

In our adjuvant Stage II breast trial, women are randomized to receive a three-month course of chemotherapy or a more standard nine-month course. QL assessments are made at frequent intervals.

We use the following instruments: 1) a patient global physical and emotional assessment; 2) a physician global physical and emotional assessment; 3) the Karnofsky Performance Status; 4) the Spitzer QL Instrument; 5) the Rand Physical and Emotional Health Status; and 6) our Breast Cancer Chemotherapy Questionnaire (BCCQ).

Instruments used to measure QL should have a number of desirable attributes: 1) it should measure both physical and emotional well being; 2) it should examine issues relevant to the patient's condition; 3) it should provide quantifiable information;

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*Abstract of a paper presented at the 10th Clinical Cancer Research Conference, held on September 30 to October 2, 1985, at Geneva Park, Lake Couchiching, Ontario.
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4) it should yield reproducible results; 5) it should be simple and easy to administer; 6) it must be credible; 7) it should be valid that is it measures what it purports to measure; and 8) it should detect a change when a true change of QL occurs (this is referred to as responsiveness).

The "signal" is the change that is detected when we administer a QL instrument on two occasions. This "signal" consists of two components: 1) true change (what we want to measure); and 2) random variation ("noise"). The best instrument for a clinical trial would be one that gives a large "signal" with relatively little "noise".

We measured the inherent variability, or "noise" in the patients in our study. As noted above, these patients receive a global physical and emotional assessment and they also submit their own physical and emotional assessment. For example, when asked how they felt physically or emotionally in the last two weeks, they can respond that they are the same, better (and if better, how much better on a 7-point scale), or worse (similarly they can indicate how much worse). We have no way of defining whether the patient is truly stable. If both the patient's and physician's global assessment agreed that the patient was the same, we assumed this reflected a stable situation. We then measured the standard deviation of the change score in the patients deemed stable by the global rating. Any variance detected in a stable patient we attribute to "noise". There is a second component of noise, which can be described as the standard deviation of the change score between patients for each degree of severity as measured by global assessment. This latter variance is not considered in our present analysis, although, we hope to do this in the future.

The ideal instrument should be the one with the maximum total "signal-to-noise" ratio.

True change in the clinical situation is measured by change on our global rating. Patients could be better or worse. Concerning our "signal-to-noise" ratio, "signal" was measured as the mean change in score for each questionnaire for all cases over a period of 14 days. "Noise" was measured as the standard deviation of the change score in stable patients. This "signal-to-noise" ratio is plotted for each clinical state.

When patients got better, the Karnofsky score started off below 0, which means that when patients seemed better, the Karnofsky scale said they were worse. The "signal-to-noise" ratio increased only slightly as patients got better. The Spitzer instrument measured slightly positive, but never approached 1.0. Our BCCQ starts off positive and increases over time and has a "signal-to-noise" ratio over 1 when patients felt better quickly.

Consversely, when patients showed minimal deterioration, the Spitzer instrument said that they were better. Our BCCQ seems to perform best for patients who became worse and, at extreme situations where the patient was worse, had the maximum "signal-to-noise" ratio. To date, instruments seem to be better at detecting patients getting worse, than those getting better.

As our "noise" signal, in patients who are stable, we have used the standard deviation of change score. In future we hope to look at the standard deviation of the change score between patients for each degree of worsening or improvement. Our "signal-to-noise" ratio is identical to delta -- the standard deviation, a major component of the sample size formula, and hence has sample size implications. The higher the ratio, the smaller the sample size required.

In summary, cancer clinical trials need evaluative instruments. Responsiveness is a major concern in this situation. The method we have presented allows us to explore the relative abilities of a number of QL instruments to detect change. To date, the number of cases we have analyzed is too small to allow any firm conclusions. However, we hope to be able to answer some of these important questions when we have accrued sufficient patients.

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OCF

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B.C. Wilson, Ph.D.
D. Wyman, Ph.D.

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M.E. McBride, M.D.
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Business Office Manager:

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Cancer Information Services:

B. Rigby, B.Sc.N., M.H.Sc.

Manager of Health Records:	**Lodge Supervisor:**
D. Armstrong	C. Stewart, R.N.

The past year has brought many changes to the Hamilton Regional Cancer Centre. Drs. Charles Catton and Curtis Johanson were welcomed to the staff of radiation oncologists.

In April, Dr. Alan Philips retired after nine years of service as a radiation oncologist.

Expansion of the Outreach Program has continued with the opening of a clinic at the Hotel Dieu Hospital, St. Catherines, under Dr. Brian Findlay. As well, we now staff a weekly follow-up clinic at the Greater Niagara General Hospital, Niagara Falls. These clinics will help to provide care closer to home for patients in the Niagara Peninsula. The Henderson clinic will continue to be the tertiary facility for the region.

Growth also is continuing in the Department of Radiation Oncology. The new 25 MeV linear accelerator came on-line in May 1985. A second rotational treatment simulator is on order; it will augment the existing Picker simulator and CT scanner and will help to improve treatment planning and quality control.

The new Lakeview Lodge, which opened in November, is providing pleasant and comfortable surroundings for out-of-town patients attending the Centre for treatment or investigation. The facility, which has 20 beds, will officially open on April 22, 1986. Carol Stewart, R.N., has joined our staff as lodge administrator.

The Cancer Information Service began operation in April of 1985. This service is described in the Special Services section.

In 1985 a functional program was developed for the Centre under the guidance of Mr. S. Isaak of the Hamilton-Wentworth District Health Council. A high point of our year was the approval of this program and the subsequent approval of funding by the Ministry of Health for a major expansion of our facility. Planning is well underway: Messrs. Isaak and Robert Price of the Centre are co-ordinating these activities. Construction will begin in late 1986.

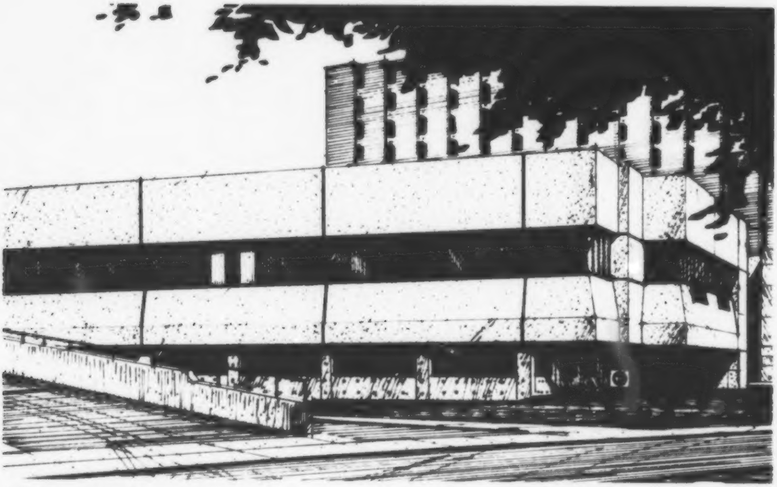
As an interim measure to relieve current overcrowding, the third floor of the new Lodge will be finished to accommodate the Clinical Trials office, the Department of Medical Oncology, and the Business Office.

The research activities at the Hamilton Regional Cancer Centre are described in the Research Programs section.

B. Rigby, B.Sc.N., M.H.Sc.
Co-ordinator, Cancer Information Services

KINGSTON REGIONAL CANCER CENTRE

KINGSTON GENERAL HOSPITAL



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V. Kraus, M.D.
W.J. Mackillop, M.B.,Ch.B.
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P.R. Galbraith, M.D.
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C. Keith, Reg.N.

Manager of Health Records:

R.S. Walker

Lodge Supervisor:

D. Broeders, Reg.N.

The year 1985 was a period of steady transformation for the Kingston Centre. The retirement of Dr. Stewart Lott from the Directorship at the end of April was followed by international search for his successor. We are delighted to report that Dr. David Ginsburg will assume this position at the beginning of 1986.

Dr. Lott's retirement and that of Dr. Winifred Ross at the end of 1985 provoked an acute shortage of radiation oncology staff. We were most grateful to Dr. Dar from the London Centre for assisting us last summer at the peak of our shortage. Fortunately, in September, Dr. Peter Dixon joined us from Manchester, England, and in November, Dr. William Mackillop came from Montreal. We shall be looking for additional staff in the months ahead, particularly as Dr. Mackillop will be spending 50% of his time in research.

We are pleased to announce that Dr. Susan Cole has joined us as a career scientist, and that, during the fall, Mrs. Dorothy Broeders assumed the position of Lodge Supervisor bringing to this post a wealth of nursing and administrative experience.

The basic research interests in Kingston now include: in vitro studies on natural and interleukin-2 activated killer cells; the application of monoclonal antibody technology to the study of drug-resistant human tumor cells; hematoporphyrin phototherapy; the in vivo assessment of protein A therapy in animal tumors; cellular heterogeneity in human tumors; and the interaction between hyperthermia and cytotoxic drugs.

The clinical physics staff continues to work on a number of programs of research and development. Currently they are installing a new control system for the Therac 20 linear accelerator to replace the original outdated one. We are working to implement an electron-beam treatment algorithm using CT scan data, and our physicists are collaborating with Dr. J.C. Kennedy in the development of a fluorescence bronchoscope.

Medical and nursing staff continue in their involvement with NCIC, OCOG and other clinical trials groups, and this may be expected to increase. We anticipate some clinical psychosocial studies in the near future. In the short term, available space within the Centre will not increase but we are reorganizing this space to better accommodate our new staff, and our expanding library facilities. We look forward to further changes in 1986, when we know the extent of new government oncology funding.

P.J. Froud, M.B.,Ch.B., D.M.R.T., F.F.R., F.R.C.P.(C)
Senior Radiation Oncologist

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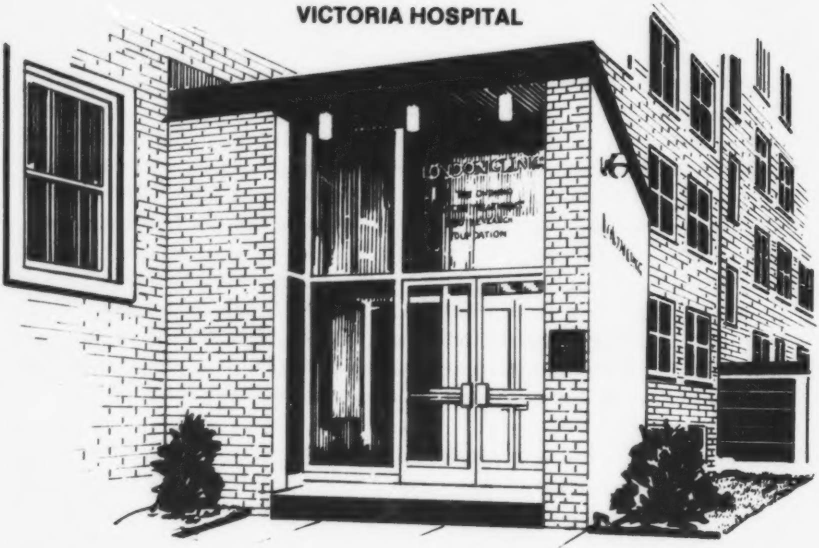
LONDON REGIONAL CANCER CENTRE

VICTORIA HOSPITAL



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A. Sawarna, M.S.W.

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Lodge Supervisor:

J. Stewart, Reg.N.

The London Regional Cancer Centre has moved into a new phase of development in 1985. In August, the Ministry of Health gave approval for the development of a new Centre on the Westminster Campus of Victoria Hospital. Funding for the project is provided by the Ministry of Health (two-thirds) and by the OCTRF, which in collaboration with the Canadian Cancer Society Ontario Division is providing funds for construction.

Planning for the new project started in September 1985 and construction will begin in the summer of 1986. The Toronto firm of Dunlop, Farrow, Aitken and Cansfield are the architects for the project. The new facilities will improve the delivery of patient care, and ensure that the Foundation will develop educational, research and patient care programs to meet regional needs into the next century.

The Foundation's Outreach Unit, at St. Joseph's Hospital, under the direction of Dr. Jamey Skillings, has increased its workload by 44% in the past year. Part of this increase derives from the use of continuous infusion devices for ambulatory patients. These chemotherapy devices reduce the number of inpatient admissions and increase the volume of ambulatory visits. Ms Nancy Keates, a grant-funded clinical trials nurse, has joined the St. Joseph's Unit. Dr. David Macdonald's neuro-oncology clinic is another development in the St. Joseph's outreach program. In 1986, all hope that an additional oncologist will be added to the St. Joseph's staff.

In 1985, Mary Jane Hodsman and Wendy Gillis initiated a nursing research project. Dr. Peter Maguire, on sabbatical from the University of Manchester, has assisted the nurse researchers and nursing staff to develop interviewing skills and to test a standard nursing history form. The nursing department has implemented a primary nursing model for medical oncology patients. In 1986, the nurse researchers will undertake a project with the Chief of Radiation Oncology to develop a primary nursing model for radiotherapy patients.

Psychosocial services have been expanded to serve the inpatient units in Victoria Hospital. An inpatient nurses support group led by London Regional Cancer Centre's social worker, Gayle Elston, has been very successful. The social work department, radiation technology, and radiation nursing have developed a patient education centre in the radiation therapy department. This drop-in centre provides education and counselling services to patients and their families. Ms Anne Sawarna based this program on a model she observed at the Memorial Sloan-Kettering Center. Ms Shelley Markland and Dr. Haydn Bush led the first widowers' support group in the autumn of 1985.

In September 1985, the Department of Radiation Oncology welcomed Dr. Peter Corbett as the new Chief of Service. Dr. Corbett is conducting a major review of regional radiation oncology services with the objective of rationalizing and improving the delivery of patient care services.

Our staff saw the Betatron, installed in 1965, replaced with a 25 MeV linear accelerator. The Therac 25 was installed, acceptance tested and placed into clinical service in 1985. This linear accelerator is being used for both x-ray and electron therapy. Another new item acquired is the MicroSelectron, which uses microsources of cesium, replacing all radium, for brachytherapy.

Dr. Vivien Bramwell was appointed Director of the Clinical Trials Unit. As a result of the dramatic expansion in workload over the past year, a Clinical Trials Protocol Review Committee was established to facilitate and rationalize the development of clinical trials. Dr. Bramwell organized the Canadian Soft Tissue Sarcoma Group to conduct, develop, co-ordinate and stimulate Canadian research in sarcomas. Drs. P. Banerjee, A. Cheung, A.R. Dar, J.A. Hammond, W. Kocha and L. Levin will initiate a Phase II study on combined radiotherapy and chemotherapy for advanced cervical cancer. Centre physicians remain committed to the development of a multidisciplinary approach to cancer treatment, research and education. Tumor board development has continued with a gynecology board, a genitourinary tumor study group, pulmonary oncology, hematology/lymphoma, sarcoma, an ear-nose-and-throat tumor board, and breast study groups.

Dr. Marjorie Wood became the co-ordinator of the palliative care team in 1985. Dr. Wood and Dr. Peter Maguire have planned the first OCTRF workshop on assessment and counselling skills relating to the psychosocial problems of patients with cancer and their families for early 1986.

A number of staff members are working together to develop a proposal for a public education department in the London Centre. This fledgling group is still defining its goals and objectives. However, they have a number of events organized already.

A successful Open House was held on Sunday, May 26, 1985. On that day, Dr. J.W. Meakin commissioned the Therac 25 in the presence of dignitaries representing the City of London, the Canadian Cancer Society, various local service groups, and the local press. The staff conducted guided tours of the Centre. Each department had special displays and its representatives were on hand to answer questions. In future this event will be held annually.

During the spring and early summer of 1985, some of the staff worked together writing, producing and editing our first television documentary, "Treating Cancer: It's Time for Change". This one-hour production was filmed in the Centre by the local Cablecast television station, but the "actors" were all the Centre's staff. The film follows the cancer patient from diagnosis to treatment, both chemotherapy and radiation. The film has been shown in London, Toronto and privately to a variety of service groups in London and the surrounding area. On each occasion a representative from the Centre is on hand to answer questions.

On August 24, 1985, a Cancer Information Day was held for the London Jaycettes. Speakers from the Centre spoke on such cancer-related issues as prevention, treatment and research into the psychosocial aspects. Other groups in the City have also requested speakers.

A staff member, representing the Centre, sits on a committee on prevention organized by the Heart and Lung Association. The Centre also has been asked to provide a liaison on an interagency council representing heart, lung and cancer prevention and treatment facilities within the City of London.

Experimental oncology now has its full complement of four career scientists, a Terry Fox clinical fellow, and a neuro-oncologist. They are working on individual and collaborative projects with a general emphasis on tumor progression, metastasis and cell differentiation. In 1985, the experimental oncologists gave 18 full-length papers, in addition to numerous abstracts and presentations at scientific meetings.

This year, Dr. J.C.F. MacDonald, Chief Physicist, retired after serving the Foundation and the London Centre since 1957. His career in medical physics spanned from the development of the first Cobalt 60 "bomb" at the London Centre to the installation and commissioning of the Therac 25 in 1985. Dr. MacDonald will act as a consultant in radiation protection during the planning and construction of the new centres in Sudbury and London.

M.J. Morrison, M.P.A.
Administrator

NORTHEASTERN ONTARIO ONCOLOGY PROGRAM*

LAURENTIAN HOSPITAL, SUDBURY

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A. Pabani, M.H.Sc., C.M.A.
(effective March 1, 1986)

Medical Oncologist:

G.D. Goss, M.B.,B.Ch.

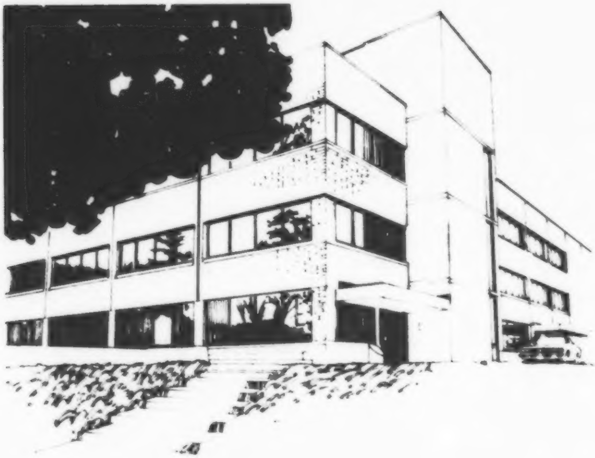
Manager of Health Records:

R. Zambelli, C.C.H.R.A.(C)
(effective March 1, 1986)

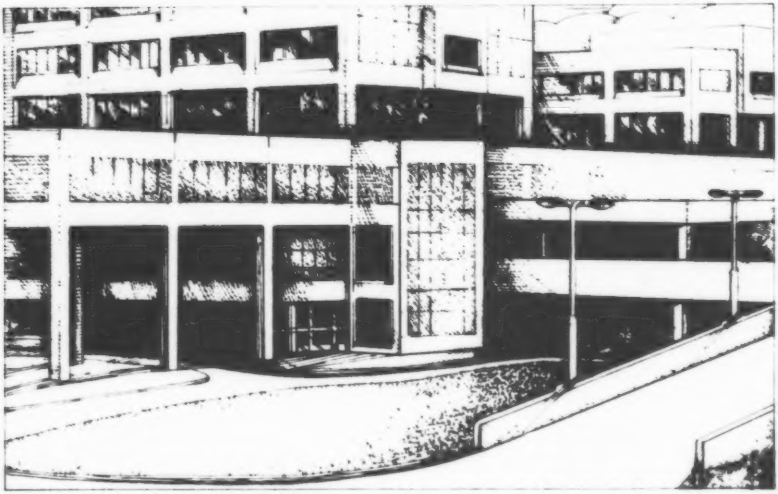
*As of September 1, 1985, the Foundation has operated an oncology program at Laurentian Hospital in Sudbury. Planning for the new regional cancer centre, to be located adjacent to Laurentian Hospital, is proceeding on schedule. We anticipate that construction will begin by the summer of 1987 and that the centre will open by mid-1989. When completed, the centre will provide facilities for radiotherapy, chemotherapy, consultation with oncologic subspecialties, research, and teaching.

OTTAWA REGIONAL CANCER CENTRE

OTTAWA CIVIC HOSPITAL



AND OTTAWA GENERAL HOSPITAL



Director:

G.E. Catton, M.B.,B.S.

Radiation Oncologists:

C.J.E. Danjoux, M.D.
L. Eapen, M.D.
P. Genest, M.D.
A.L. Girard, M.D.
R.S.R. McDermot, M.D.
B.D. Nair, M.B.,B.S.

Medical Oncologists:

C. Cripps, M.D.
W.K. Evans, M.D.
W.E. Hirte, M.D.
J.A. Maroun, M.D.
D.J. Perrault, M.D.
D.J. Stewart, M.D.
S. Verma, M.D.
V.P.J. Young, M.D.

Clinical Assistants:

M. Allen, M.D.
H. Bastianelli, M.D.
K.R. Hopkinson, M.D.
I.A. Prosser, M.D.
B.V. Reddy, M.D.
K. Robillard, M.D.

Career Scientists:

H.C. Birnboim, M.D.
R.G. Liteplo, Ph.D.

Physicists:

L.H. Gerig, Ph.D.
P.M. Phalzner, M.Sc.
G.P. Raaphorst, Ph.D.

Business Manager:

S. McAdam

Executive Secretary:

D. Pineau, C.M.S.

Nurse Administrator:

C.J. MacMillan, B.Sc.N.

Head Nurse (General Division)

L. Fawcett, R.N.

Senior Radiotherapy Technician:

R.P. Wallace, A.C.(T.)

Managers of Health Records:

M.C. Therrien (Civic Hospital Division)
M.M. Brassard (General Hospital Division)

Lodge Supervisor:

J.M. Davidson, R.N.

During the past year several staff changes have taken place. Dr. Robert G. Liteplo has become the second career scientist in the Department of Experimental Oncology. He joined Dr. H.C. Birnboim at the General Division on May 1, 1985. Dr. G. Peter Raaphorst, joined the staff as Chief Physicist in September. Dr. William K. Evans took up his appointment as Chief of Medical Oncology on November 1. Dr. Wolfgang E. Hirte retired in October after 13 years of service in medical oncology. Dr. Shailendra Verma joined the staff as a medical oncologist in July. Also, in July, we said goodbye to Dr. Pierre Drouin who has moved to Notre Dame Hospital and became Director of the Division of Gynecology-Oncology at the University of Montreal. In his place we welcome Dr. Michel Prefontaine; a graduate of University of Montreal, he interned at St. Mary's Hospital, Montreal and trained in gynecology/oncology at Toronto General Hospital, the Princess Margaret Hospital in Toronto, and the Henderson General Hospital in Hamilton.

In October, Angeline Minor (General Division -- Switchboard) was honored on the occasion of 25 years of service with the Foundation. The staff of the Health Records Department, Civic Division, presented Connie Therrien with a plaque to mark her silver anniversary with the Foundation.

Dr. Cyril Danjoux was appointed Head of Radiation Oncology, Civic Division, in November 1984, and Dr. Andre Girard became Director of the Radiation Oncology Training Program on January 1, 1985.

On November 2, 1984, Joan Lyons, Ann Archibald, Dorothy Parker and Faye Copeland were honored with long-service awards. At a ceremony at his office, Dr. Catton presented cheques and extended congratulations on behalf of the Foundation.

The secretarial and accounting staff are delighted with their new IBM PC word processors. All received introductory training in early November before the equipment was installed.

On April 22, 1985, a symposium "Controversies in Breast Cancer" was held in Ottawa and constituted the scientific portion of the NCIC meeting.

In May 1985, Dr. S. Jackson of the Cancer Control Agency of British Columbia gave two lectures as a Vail Visiting Professor. His presentations were entitled "The use of the Selectron in the treatment of carcinoma of the cervix" and "The B.C. experience with interstitial implant in carcinoma of the tongue".

Drs. David Stewart and Wolfgang Hirte attended the 14th International Congress of Chemotherapy in Kyoto, Japan, between June 18 and 24, 1985.

In June 1984, the Department of Experimental Oncology became operative at the Ottawa Regional Cancer Centre. The head of this department, Dr. H.C. Birnboim, joined the Centre's staff from the Chalk River Nuclear Laboratories of Atomic Energy of Canada Ltd. Previously the research laboratory had been used by other members of the clinical staff, principally Drs. D.J. Stewart and J. Maroun. With the initiation of a career scientist program in Ottawa, the existing laboratory facilities were upgraded for more active use. At the General Division laboratory, an existing autoclave was put into service, a new glassware washer and dryer, and a new ice machine were installed and a still and deionizer were upgraded to supply pure water. Also, a new coldroom was installed and a small darkroom was organized. New shelving and drawer space were added to accommodate supplies for new department activities. The second laboratory is located at the Civic Division.

In support of hyperthermia research at the Ottawa Regional Cancer Centre we have adapted for clinical use a computerized thermometry data acquisition system which controls the microwave applicator. We have perfected the use of multiple thermocouple probes for temperature measurement and display during the treatment. In collaboration with the National Research Council (NRC), animal experiments are being done using the 2450 MHz unit, and the Princess Margaret Hospital's ultrasound system.

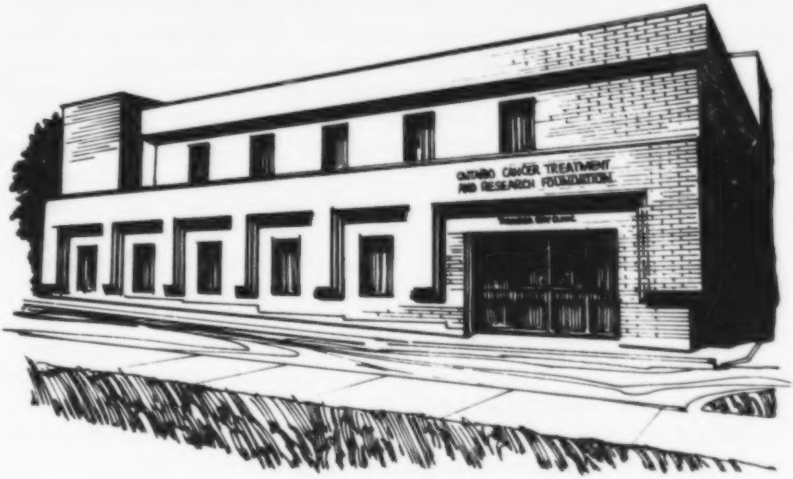
We are collaborating with the NRC in designing new 2450 MHz applicators and also a 915 MHz generator with various applicators. So far we have treated two patients with a combination of radiotherapy and hyperthermia. In the coming year we hope to establish a hyperthermia biology laboratory, to continue with physics research in hyperthermia, to develop an interstitial hyperthermia unit, and to continue collaboration with the NRC, Atomic Energy of Canada Ltd., and Carleton University.

With the growing interest in the application of interstitial implants in the management of primary brain tumors, we look forward to the return of Dr. Vasco DaSilva, a neurosurgeon, who has been studying this technique in California. Initially, the Ottawa Neuro-Oncology Group intend to assess the feasibility of temporary high-activity Iodine-125 implants in conjunction with external beam radiation for the treatment of high-grade astrocytomas. The first patient had such an implant in November 1985 and, to date, 4 patients have been so treated. The feasibility study will involve 10 patients, who will be monitored to detect technical difficulties and/or toxicity. After this we will embark on a Phase I-II trial to study interstitial brain implants in conjunction with external-beam radiation and intracarotid chemotherapy for the high-risk brain tumors.

G.E. Catton, M.B.,B.S., D.M.R.T., F.R.C.P.(C)
Director

THUNDER BAY REGIONAL CANCER CENTRE

GENERAL HOSPITAL OF PORT ARTHUR



Director:

J.F. Kotalik, M.D.

Radiation Oncologists:

S. Gulavita, M.B.,B.S.
M. McLean, M.B.,B.Ch.

Medical Oncologist:

S.D. Zaentz, M.D.

Clinical Assistant:

J.E.A. McKnight, M.B.,B.Ch.

Physicists:

M. Al-Ghazi, Ph.D.
P.D. Sharma, M.Sc.

Business Manager:

M.M. Ryan

Senior Nurse:

L. Bright, Reg.N.

Supervisory Radiotherapy Technician:

J.V. Morgan, R.T.

Nurse Social Worker:

V. Coley, Reg.N.

Manager of Health Records:

M.P. Winfield, C.C.H.R.A.(A)

Lodge Supervisor:

M. Magnusson

The year 1985 was a busy and difficult one and the Centre underwent some important changes. In July, Dr. Donald Zaentz joined the Centre as a full-time medical oncologist bringing with him from Iowa considerable experience in patient care and clinical research. It means that for the first time in three years again we have a full-time medical oncologist. During the summer Dr. Fritz Hellmuth decided to return to Winnipeg to pursue his non-medical interests and we had no immediate replacement for him. Drs. Hargan, Goodyear, Yosef from Glasgow, and Maus from Windsor provided part-time and locum assistance. Before the year was over, however, Dr. Michael McLean arrived from England to become our radiation oncoligst, and his wife, Dr. Arlene McKnight, accepted the position of clinical assistant. Dr. Sunil Gulavita also joined us as an additional full-time oncologist. These additions to the staff freed Dr. Judy Chalykoff, our clinical assistant for the past five years, to pursue her interest in palliative care. We will continue to support her practice in and outside of the Centre in the coming years. Dr. Matthew Al-Ghazi, after completing his training in London, Ontario, was appointed to our Centre as a physicist.

The major event of the year was the arrival and installation of a dual-energy 6 and 20 MeV Siemens linear accelerator. This required extensive renovation of the treatment area. The unit has behaved well during the stage of calibration and the formal opening is expected in January 1986. This addition will give our Centre full high-energy and electron capability and should all but eliminate the need to refer patients for radiotherapy outside the Centre. This new capacity will also stimulate research in medical physics.

Further effort has been put into the development of clinical trials, this time including Phase II studies (a report of this activity appears in the Research Programs section in this publication). In co-operation with the Departments of Psychology, Sociology, Nursing and Social Studies of Lakehead University, we established a Psychosocial Oncology Working Group with the goal of developing a research program in this important area. Dr. David Osoba made a presentation to one of the early meetings of this group. We have undertaken one retrospective and one prospective study in this field.

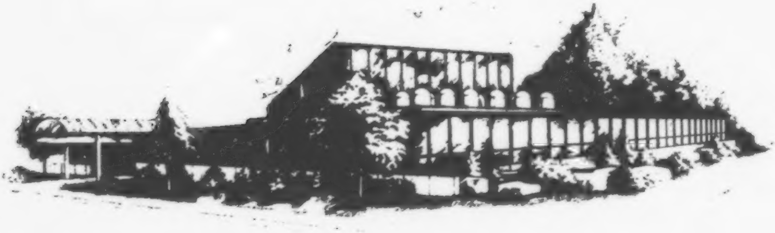
At the end of 1985, the Thunder Bay Centre finally had a full complement of physicians and physicists. It has the most up-to-date treatment unit, which will allow us to expand service, research and education in the coming year. In the meantime, however, we struggle with a critical space shortage and we have had to rent offices from our host hospital in an adjacent building. We have started the planning process which will lay the groundwork for future expansion.

J.F. Kotalik, M.D., D.M.R.T., F.R.C.P.(C)
Director

OCF

TORONTO-BAYVIEW REGIONAL CANCER CENTRE

SUNNYBROOK MEDICAL CENTRE



Director:

R.D.T. Jenkin, M.B.,B.S.

Radiation Oncologists:

I. Ackerman, M.D.
M.P. Berry, M.B.,B.S.
P.A. Catton, M.D.
R.G. MacKenzie, M.D.
N.D. Mountifield, M.D.
C.S. Young, M.D.

Medical Oncologists:

R.A.A. Buckman, M.B.,B.Ch.
N. Iscoe, M.D.
I.J. Kerr, M.D.
D. Osoba, M.D.
J.J. Rusthoven, M.D.
D.J.A. Sutherland, M.D.

Clinical Assistants:

H.M. Kocandrle, M.D.
J.A. MacKinnon, M.D.
T.B. McQuiston, M.D.

Physicists:

H.B. Michaels, Ph.D.
P.F. O'Brien, M.Sc.
R.A. Siwek, Ph.D.

Administrator:

H.B. Wodinsky, M.H.Sc.

Administrative Assistant:

K.A. Nicholson

Business Manager:

G.B. Kolos, B.A.,B.Ed.

Nurse Administrator:

C. Johnston, Reg.N.

Chief Radiotherapy Technologist:

S.V. Scott, A.C.(T), R.T.R.

Manager of Health Records:

M. Mistruzzi, C.C.H.R.A.(C)

The growth of Toronto-Bayview Regional Cancer Centre (T-BRCC), the Foundation's newest functioning centre, continued in 1985. The planned facility size of 2500 new patients per year was achieved. The annualized rate of total patient visits increased to approximately 40,000, of which 59% were for radiation treatment or planning, 30% for follow-up visits, 6% new patient visits, and 6% visits to receive chemotherapy. The success was evident of the policy of decentralizing the giving of chemotherapy. The demand for radiation will continue to grow rapidly because this treatment is centralized in the centre and the T-BRCC will continue to absorb, for the whole of Metropolitan Toronto, the annual increment in numbers of cancer patients who require such treatment. This situation will not ease until a third centre begins to functions in Metropolitan Toronto, that is, about 1990. By that time we anticipate that our new patient registrations will be not less than 4000 per year.

The T-BRCC is the outpatient component of the regional cancer program at Sunnybrook Medical Centre (SMC). Our medical and radiation oncologists care for 79 inpatients in an acute-care oncology unit. The growth of this regional cancer program has placed under severe stress the available resources for inpatients, outpatients and the required support services. The SMC and the T-BRCC have made a common submission to the Ministry of Health with regard to our needs for the next five years.

Our four-year old outpatient facility underwent major renovations to meet the increased tasks. Four new doctors' offices were added; the library was moved and the administrative offices moved and enlarged. A new lecture theatre and office space for the primary nurses was constructed in previously unused basement space. Once again, funding was not available to develop 'wet' laboratory research space.

The staff grew to 129 full-time employees. Drs. Nigel Mountifield and Charlene Young joined the Division of Radiation Oncology and Robert Buckman, the Division of Medical Oncology. At the start of the year, Harold Wodinsky became the new administrator. George Kolos became the new business manager. Sandra Scott became the Head of the Department of Radiotherapy Technology.

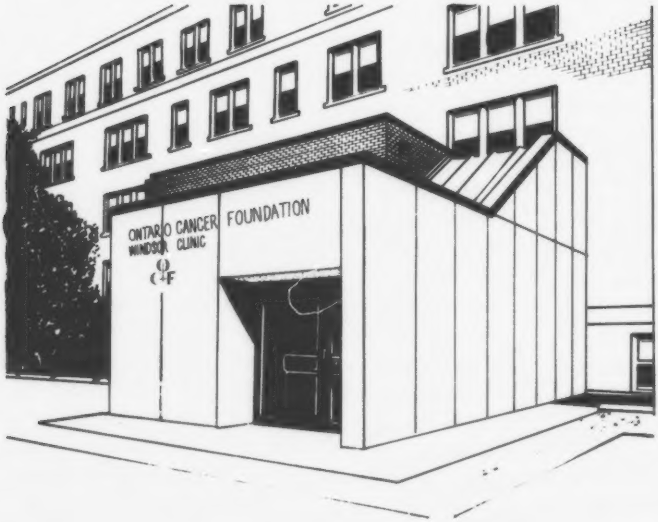
Our second 25 MeV accelerator was installed in 1985 and since the summer has been on loan to PMH until a similar machine has been installed at that facility.

Other than our unused research space, the T-BRCC facility came into full use in 1985 and thus we completed a major step in our evolution.

R.D.T. Jenkin, M.B.,B.S., F.R.C.P.(C)
Director

WINDSOR REGIONAL CANCER CENTRE

METROPOLITAN GENERAL HOSPITAL


ONTARIO CANCER FOUNDATION
WINDSOR CLINIC
OCF

Director:

G.C.K. Mok, M.D.

Radiation Oncologist:

C.D. Springer, M.B.,B.S.

Medical Oncologists:

H.T. Abu-Zahra, M.B.,B.Ch.
D.B. McDonald, M.D.
S. Yoshida, M.D.

Clinical Assistant:

M. Foote, M.D.

Physicist:

D. Smocovitis, M.Sc.

Business Manager:

E. Schwindt

Senior Radiotherapy Technician:

R. Macpherson Todd, R.T.

Senior Nurses:

A. Beaton, Reg.N.
M. O'Neill, Reg.N.

Manager of Health Records:

R. Van Der Borgh

In 1985, there were several important staff changes. Dr. John Maus retired on June 30. He returned in mid-August to take up a post as locum tenens in radiation oncology for one month. Dr. Colvin Springer joined the Centre as a radiation oncologist in July. Dr. Margaret Foote became a full-time clinical assistant in the radiation oncology service on September 1. Mrs. Viola Gignac retired after 27 years of service as manager of our health records; Miss Rita Van Der Borgh has succeeded her in this position. Dr. George C.K. Mok was appointed Director of the Centre effective July 1.

The medical oncologists continue their association with the Wayne State University to participate in the SWOG, NCIC, and OCOG clinical trials. The workload is extremely heavy. We have had no success in recruiting a fourth medical oncologist for the Centre.

With respect to workload, we expect the number of new cases to be the same or slightly higher than 1984. Again, due to restriction in employment of new staff, the nursing staff in medical oncology often have to work overtime and, in other areas, staff have to "double up".

In August, the Windsor Centre was given permission to proceed with the building of a bunker for installation of a dual-energy linear accelerator. We look forward to treating patients with this new equipment in the fall of 1986.

G.C.K. Mok, M.D.
Director

SERVICE LOAD

The following tables describe the service load of the Foundation's seven regional cancer centres during the calendar year 1984.

In 1984, 43,948 patients were seen at the Foundation's regional cancer centres. Of these, 92% had malignant lesions and, of these lesions, 11,990 were new to the centres (Table I). Of cases referred for non-malignant conditions, 84% were first seen in 1984 (Table II). The majority of these, 1642, were seen in consultation. In all, 9042 cancer cases were treated by radiotherapy (Table III); of these, 4088 were treated by cobalt units, 3431 by a linear accelerator, and 1523 by other methods of radiotherapy.

During the year, patients made 408,433 visits to the regional cancer centres and the majority, 399,126, were for treatment of malignant disease (Table IV). Of all radiation treatments, 82% were given on an outpatient basis (Table V).

As of January 1, 1982, with the implementation of the Patient Care Management System in the centres, it has been possible to retrieve data in more detail than was possible in previous years. However, the system has not been implemented completely and hence the tabulations are marked "provisional". It must be emphasized that these tables are comparable only with the service load tables published for 1982 and 1983; they are not comparable with those for the years before this. Also, they are not comparable with the data for the fiscal year presented for the Princess Margaret Hospital.

As the data began to be captured on-line in 1985, errors were found in the tables published in *Cancer in Ontario* 1983 and 1984, giving the number of cases treated during 1982 and 1983 by method of radiotherapy. For completeness, these revised tables are included as Tables IIIA and IIIB respectively.

TABLE I*

Malignant Caseload During 1984[1]

TREATMENT CENTRE	TREATED				SEEN FOR CONSULTATION OR FOLLOW-UP	TOTAL
	Radiation	Radiation and Chemotherapy	Chemotherapy and/or Immunotherapy	Other		
	Cases New in Current Year					
Hamilton	1,008	140	421	27	969	2,565
Kingston	440	79	91	46	369	1,025
London	1,065	183	354	153	924	2,679
Ottawa	917	188	343	123	1,083	2,654
Thunder Bay	182	28	57	2	180	449
Toronto-Bayview	691	166	144	223	472	1,696
Windsor	299	64	208	5	346	922
TOTAL	4,602	848	1,618	579	4,343	11,990
	Cases Registered in any Previous Year					
Hamilton	320	145	756	11	4,620	5,852
Kingston	163	98	243	145	2,472	3,121
London	289	239	506	192	5,433	6,659
Ottawa	324	275	786	158	5,839	7,382
Thunder Bay	64	34	127	3	1,055	1,283
Toronto-Bayview	122	96	183	36	977	1,414
Windsor	83	69	393	29	2,267	2,841
TOTAL	1,365	956	2,994	574	22,663	28,552
TOTAL ALL MALIGNANT	5,967	1,804	4,612	1,153	27,006	40,542

* Provisional (transition period — see text)

[1] Includes cases seen at peripheral clinics.

TABLE II*

Other (Non-Malignant) Caseload During 1984[1]

TREATMENT CENTRE	TREATED				SEEN FOR CONSULTATION OR FOLLOW-UP	TOTAL
	Radiation	Radiation and Chemotherapy	Chemotherapy and/or Immunotherapy	Other		
	Cases New in Current Year					
Hamilton	13	—	15	7	253	288
Kingston	25	—	32	54	221	332
London	66	1	120	302	519	1.008
Ottawa	38	—	6	171	152	367
Thunder Bay	7	—	2	3	48	60
Toronto-Bayview	5	—	2	291	263	561
Windsor	6	—	46	2	186	240
TOTAL	160	1	223	830	1.642	2.856
	Cases Registered in any Previous Year					
Hamilton	—	—	—	—	18	18
Kingston	1	—	—	4	42	47
London	2	—	3	—	105	110
Ottawa	2	1	4	11	94	112
Thunder Bay	1	—	—	—	13	14
Toronto-Bayview	1	—	3	22	201	227
Windsor	—	—	2	—	20	22
TOTAL	7	1	12	37	493	550
TOTAL OTHER	167	2	235	867	2.135	3.406

* Provisional (transition period — see text)

[1] Includes cases seen at peripheral clinics.

TABLE III*

Cases Treated During 1984 by Method of Radiotherapy

METHOD OF TREATMENT	HAMILTON	KINGSTON	LONDON	OTTAWA	THUNDER BAY	TORONTO BAYVIEW	WINDSOR	TOTAL
	Malignant Neoplasms							
Superficial x-ray	154	151	136	29	30	48	—	548
Deep x-ray	70	16	—	—	9	2	109	206
Cobalt^{60}	1,061	387	487	970	268	499	416	4,088
Cesium^{137}	—	—	20	—	—	—	—	20
Betatron	—	—	278	—	—	—	—	278
Linear accelerator	430	383	1,037	906	—	675	—	3,431
Intracavitary	24	17	80	52	11	6	36	226
Interstitial	13	9	15	2	4	2	—	45
Moulds and applicators	—	—	9	147	—	—	—	156
Systemic isotopes	—	2	—	—	—	—	—	2
Others	8	—	11	16	—	7	—	42
SUB-TOTAL	1,760	965	2,073	2,122	322	1,239	561	9,042
	Other Non-Malignant							
Superficial x-ray	2	8	34	2	5	—	—	51
Deep x-ray	—	—	—	—	—	—	1	1
Cobalt^{60}	8	8	10	31	3	4	—	64
Cesium^{137}	—	—	—	—	—	—	—	—
Betatron	—	—	—	—	—	—	—	—
Linear accelerator	3	2	12	9	—	3	—	29
Intracavitary	—	—	2	2	—	—	—	4
Interstitial	—	—	—	—	—	—	—	—
Moulds and applicators	—	—	3	1	—	—	—	4
Systemic isotopes	—	8	—	—	—	—	—	8
Others	—	—	9	—	—	—	—	9
SUB-TOTAL	13	26	70	45	8	7	1	170
TOTAL[1]	1,773	991	2,143	2,167	330	1,246	562	9,212

* Provisional (transition period — see text)

[1] A case can be treated by more than one method per year.

TABLE IIIA*

Cases Treated During 1983 by Method of Radiotherapy

METHOD OF TREATMENT	HAMILTON	KINGSTON	LONDON	OTTAWA	THUNDER BAY	TORONTO BAYVIEW	WINDSOR	TOTAL
	Malignant Neoplasms							
Superficial x-ray	283	188	120	31	33	30	—	685
Deep x-ray	73	57	—	—	20	4	119	273
Cobalt^{60}	1.084	430	513	910	266	490	410	4.103
Cesium^{137}	—	1	2	—	2	—	—	5
Betatron	—	—	388	—	—	2	—	390
Linear accelerator	512	380	934	912	—	307	—	3.045
Intracavitary	44	26	92	46	13	—	35	256
Interstitial	—	7	44	4	2	1	1	59
Moulds and applicators	—	—	13	92	—	—	—	105
Systemic isotopes	—	—	—	—	—	—	—	—
Others	—	—	2	—	—	—	—	2
SUB-TOTAL	1.996	1.089	2.108	1.995	336	834	565	8.923
	Other Non-Malignant							
Superficial x-ray	19	6	36	—	9	—	—	70
Deep x-ray	—	2	—	—	—	—	12	14
Cobalt^{60}	17	5	14	8	5	4	2	55
Cesium^{137}	—	—	—	—	—	—	—	—
Betatron	—	—	1	—	—	—	—	1
Linear accelerator	5	5	18	2	—	4	—	34
Intracavitary	—	3	—	—	—	—	—	3
Interstitial	—	—	—	—	—	—	—	—
Moulds and applicators	—	—	—	—	—	—	—	—
Systemic isotopes	—	—	—	—	—	—	—	—
Others	—	—	10	—	—	—	—	10
SUB-TOTAL	41	21	79	10	14	8	14	187
TOTAL[1]	2.037	1.110	2.187	2.005	350	842	579	9.110

* Provisional (transition period — see text): this table replaces Table III in *Cancer in Ontario*. 1984.

[1] A case can be treated by more than one method per year.

TABLE IIIB*

Cases Treated During 1982 by Method of Radiotherapy

METHOD OF TREATMENT	HAMILTON	KINGSTON	LONDON	OTTAWA	THUNDER BAY	TORONTO BAYVIEW	WINDSOR	TOTAL
	Malignant Neoplasms							
Superficial x-ray	352	151	117	17	38	6	—	681
Deep x-ray	69	30	—	—	20	6	127	252
Cobalt^{60}	1,018	367	714	876	298	346	382	4,001
Cesium^{137}	—	—	3	—	—	—	—	3
Betatron	1	—	427	—	1	—	—	429
Linear accelerator	425	391	731	714	—	75	1	2,337
Intracavitary	64	22	118	40	14	1	34	293
Interstitial	2	7	32	—	4	10	—	55
Moulds and applicators	—	—	11	—	—	—	—	11
Systemic isotopes	—	1	—	—	—	—	—	1
Others	—	—	1	—	—	—	—	1
SUB-TOTAL	1,931	969	2,154	1,647	375	444	544	8,064
	Other Non-Malignant							
Superficial x-ray	23	8	60	—	21	—	—	112
Deep x-ray	—	—	—	—	—	1	3	4
Cobalt^{60}	6	8	12	4	3	2	6	41
Cesium^{137}	—	—	—	—	—	—	—	—
Betatron	—	—	3	—	—	1	—	4
Linear accelerator	2	3	15	4	—	—	—	24
Intracavitary	—	—	—	—	—	—	—	—
Interstitial	—	—	2	—	—	—	—	2
Moulds and applicators	—	—	—	—	—	—	—	—
Systemic isotopes	—	—	—	—	—	—	—	—
Others	—	—	4	—	—	—	—	4
SUB-TOTAL	31	19	96	8	24	4	9	191
TOTAL[1]	1,962	988	2,250	1,655	399	448	553	8,255

* Provisional (transition period — see text); this table replaces Table III in *Cancer in Ontario*, 1983

[1] A case can be treated by more than one method per year.

TABLE IV*

Service Load, 1984

TREATMENT CENTRE	VISITS FOR					TOTAL VISITS
	Treatment			Non-Treatment		
	Radiation	Chemotherapy Immunotherapy	Other	Simulation	Consultation or Follow-up	
	Visits for Malignant Neoplasms					
Hamilton	24,123	10,600	479	2,740	38,688	76,630
Kingston	13,213	2,657	752	1,653	16,342	34,617
London	30,960	7,330	837	2,719	36,005	77,851
Ottawa	30,851	11,761	1,411	2,619	54,418	101,060
Thunder Bay	5,959	1,566	187	320	7,432	15,464
Toronto-Bayview	15,701	3,618	916	1,687	27,934	49,856
Windsor	10,154	7,491	538	1,128	24,337	43,648
TOTAL	130,961	45,023	5,120	12,866	205,156	399,126
	Other Non-Malignant					
Hamilton	120	23	64	17	536	760
Kingston	131	45	177	22	777	1,152
London	460	168	412	67	1,822	2,929
Ottawa	433	52	382	47	787	1,701
Thunder Bay	73	22	7	4	194	300
Toronto-Bayview	132	12	381	8	1,155	1,688
Windsor	31	149	70	6	521	777
TOTAL	1,380	471	1,493	171	5,792	9,307
TOTAL ALL VISITS	132,341	45,494	6,613	13,037	210,948	408,433

*Provisional (transition period — see text)

TABLE V*

Treatments by Radiation During 1984, In-Patients and Out-Patients

METHOD OF TREATMENT	HAMILTON		KINGSTON		LONDON		OTTAWA		THUNDER BAY		TORONTO BAYVIEW		WINDSOR		TOTAL	
	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out
Malignant Neoplasms																
Superficial x-ray	20	724	5	701	46	848	45	216	5	206	—	342	—	—	121	3.037
Deep x-ray	29	221	10	[illegible]	—	—	—	—	8	55	—	20	93	1.249	140	1.610
Cobalt^{60}	1.879	12.890	1.817	4.700	1.493	7.693	2.956	12.980	1.331	4.334	1.286	4.826	1.617	7.140	12.379	54.563
Cesium^{137}	—	—	—	—	1:128	—	—	—	—	—	—	—	—	—	1.128	—
Betatron	—	—	—	—	318	3.326	—	—	—	—	—	—	—	—	318	3.326
Linear accelerator	693	7.593	754	5.129	4.277	11.688	1.899	12.479	—	—	1.732	7.445	—	—	9.355	44.334
Intracavitary	35	—	21	—	88	—	69	—	16	—	6	—	55	—	290	—
Interstitial	6	7	8	1	2	13	2	—	4	—	2	—	—	—	24	21
Moulds and applicators	—	—	—	—	1	8	1	147	—	—	—	—	—	—	2	155
Systemic isotopes	—	—	1	1	—	—	—	—	—	—	—	—	—	—	1	1
**Others	7	19	—	—	6	25	4	53	—	—	5	37	—	—	22	134
SUB-TOTAL	2.669	21.454	2.616	10.597	7.359	23.601	4.976	25.875	1.364	4.595	3.031	12.670	1.765	8.389	23.780	107.181
Other Non-Malignant																
Superficial x-ray	—	4	—	23	—	64	—	25	—	18	—	—	—	—	—	134
Deep x-ray	—	—	—	—	—	—	—	—	—	—	—	—	3	28	3	28
Cobalt^{60}	—	62	10	45	25	107	—	296	10	45	—	54	—	—	45	609
Cesium^{137}	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Betatron	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Linear accelerator	—	54	—	44	38	187	5	104	—	—	—	78	—	—	43	467
Intracavitary	—	—	—	—	2	—	2	—	—	—	—	—	—	—	4	—
Interstitial	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Moulds and applicators	—	—	—	—	—	4	—	1	—	—	—	—	—	—	—	5
Systemic isotopes	—	—	—	9	—	—	—	—	—	—	—	—	—	—	—	9
**Others	—	—	—	—	—	33	—	—	—	—	—	—	—	—	—	33
SUB-TOTAL	—	120	10	121	65	395	7	426	10	63	—	132	3	28	95	1.285
TOTAL OF ALL TREATMENTS	2.669	21.574	2.626	10.718	7.424	23.996	4.983	26.301	1.374	4.658	3.031	12.802	1.768	8.417	23.875	108.466

* Provisional (transition period — see text)

** Others include radiation codes unknown.

ONTARIO CANCER INSTITUTE

incorporating

PRINCESS MARGARET HOSPITAL

Director:

R. S. Bush, M.D.

Medical Oncology (Clinical and Research):

R.E. Alison, M.D.
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R. Corringham, M.B.,B.S.
J.E. Curtis, M.D.
C. Erlichman, M.D.
R. Feld, M.D.
S. Fine, M.D.
R. Hasselback, M.D.,C.M.
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J.F.G. Sturgeon, M.B.,B.S.
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P.Y. Poon, M.B.,B.S.
D.F. Rideout, M.B.,B.S.

Nuclear Medicine:

G.N. Ege, M.D.

Pathology:

C. Bergeron, M.D.
T.C. Brown, M.D.
J.S. Carruthers, M.D.
V.L. Fornasier, M.D.
G.J. Laroye, M.D.
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M.E. Platts, M.D.
L.M. Sugar, M.D.
T. Treger, M.D.

Microbiology:

P.G. Tuffnell, M.D.

Physics (Clinical and Research):

H. Alasti-Hamed, M.Sc.
M.C. Archer, Ph.D.
M.J. Bronskill, Ph.D.
J.R. Cunningham, Ph.D.
A. Fenster, Ph.D.
S. Foster, Ph.D.
D.M. Galbraith, B.Sc.
J. Grant, M.Sc.
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J. Jezioranski, M.Sc.
P.M.K. Leung, Ph.D.
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A.M. Rauth, Ph.D.
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A. Bernstein, Ph.D.
R. Buick, Ph.D.
A. Ciampi, Ph.D.
A.J. Cunningham, Ph.D.
R.M. Gorczynski, Ph.D.
R. Gronostajski, Ph.D.
N. Hozumi, Ph.D.
V. Ling, Ph.D.
H. Llewellyn-Thomas, Ph.D.
T.W. Mak, Ph.D.
E.A. McCulloch, M.D.
R.G. Miller, Ph.D.
S. Minkin, Ph.D.
N. Miyamoto, Ph.D.
R.A. Phillips, Ph.D.
J.E. Till, Ph.D.
D. Tritchler, Ph.D.

Biostatistics:

G. DeBoer, Ph.D.
D. Tritchler, Ph.D.

Administrator:

J.E. Ratz

Assistant Administrators:

E. Govoni
J.P. Holder, Reg.N.
T.J.D. West
W. Wilkinson

Manager of Health Records:

A. Buchanan, B.A., C.C.H.R.A.(C)

Librarian:

C. Morrison, B.A., M.L.S.

During the past year, the Ontario Cancer Institute incorporating the Princess Margaret Hospital reached a critical crossroad; one road leads downhill to deterioration, the other uphill to continued excellence. Throughout the year, major efforts were made to ensure that this Institute stays on the high road.

While continuing to cope with difficult patient loads, medical, scientific and administrative staff, in conjunction with the Ontario Cancer Treatment and Research Foundation, devoted much time and effort to a second Role Study, which sought ways to meet current and future patient needs within a comprehensive cancer program.

In December the Role Study was presented to the Minister of Health, and in early January the critical needs of the Ontario cancer control system will be made public. Senior OCI/PMH administrative staff will hold discussions with the Ministry concerning the most appropriate way of resolving the urgent problems at OCI/PMH.

During the past year the acute shortage of treatment facilities was compounded when the 26-year-old Betatron was taken out of service. Renovations are underway to install a Therac 25 which we expect will be in operation by the summer of 1986. In the interim, the OCI/PMH staff and machines could not cope with the overflow patients and a Therac 25 at Toronto-Bayview Regional Cancer Centre has been made available to our patients. This arrangement ensures that our patients will receive treatment but it creates many difficulties in scheduling because patients and their paperwork have to be transported back and forth between the two facilities.

In addition to renovation for the new Therac 25, an area in the northwest wing is being expanded to provide urgently needed space to replace two cobalt machines, additional office and work space for the radiotherapy department and mould room, and space for an upgraded magnetic resonance imaging machine. Although this expansion will provide additional breathing room, minor changes will not provide the major increases recommended in the Role Study.

Despite these handicaps, the OCI/PMH staff have participated in many evaluation programs to ensure that we meet high standards in our clinical, research and administrative programs. In the fall of 1985, the hospital underwent a preaccreditation survey in preparation for a full survey by the Canadian Council on Hospital Accreditation in the fall of 1986. The surveyors recognized the unique status of the PMH and commended the staff on many of its activities including the development of a quality assurance program. The OCI/PMH School for Therapy Radiographers has been granted accreditation and received a full five-year award in recognition of the outstanding training it provides for students from across Canada.

The hospital continues to support its outreach program for patients and physicians living far from Toronto. During the past year, our physicians travelled on a rotating basis to six peripheral clinics. The new oncology program in Sudbury under the full-time direction of Dr. R. Corringham will do much to provide diagnostic, treatment and follow-up services in Northeastern Ontario.

We are pleased to announce that several highly skilled individuals have joined our staff during the past year. Dr. William Duncan from the University of Edinburgh, Scotland, is the new head of radiation oncology. Drs. B. O'Sullivan and N.J. Laperriere from McGill University also joined that department, and Dr. J.H. Meharchand has joined the Department of Medicine. With regret we note that Dr. A.R. Harwood has left to practice in the United States and that Dr. Thomas C. Brown has retired after 28 years service in pathology.

The past year has been one of transition and renewal in the Division of Biological Research. Three senior scientists have left to provide leadership at other institutions; Drs. A. Bernstein and N. Hozumi moved their laboratories to the new Mount Sinai Research Institute, and Dr. A. Ciampi has become a senior statistician at McGill University. However, four new appointments will strengthen the commitment of the Division to a union of cellular and molecular approaches to the study of growth and differentiation in normal and malignant cells.

The new investigators, Drs. Richard Gronostajski and Neil Miyamoto, are taking their first independent posts. Both are well trained in molecular biology but retain firm roots in cellular function. Their individual research plans are mutually complementary because both work in the area of the control of gene expression – a field that relates closely to the work of several other investigators in the Division.

The third appointee, Dr. Norman Iscove, obtained his Ph.D. at OCI but will return in the spring of 1986 after almost a decade at the Basel Institute of Immunology. He has an international reputation in the study of the action of hemopoietic growth factors, and his experience, at both the molecular and cellular levels, will support other hematological research in progress within the Division.

Dr. Salomon Minkin has joined the Division from York University. His special knowledge of biostatistics strengthens the division's commitment to research in medical informatics.

These new appointments will strengthen the Canadian science generally, but particularly the area of biomedical research.

The OCI/PMH's contribution to clinical and scientific research was recognized through many awards presented to staff and by invitations to deliver lectures at conferences, universities and hospitals around the world. This year the Institute published a general Annual Report, and a separate Clinical and Research Report. This second report documents the research projects and clinical trials underway at OCI/PMH and lists the hundreds of papers published and lectures delivered.

R.S. Bush, M.D., F.R.C.P.(C)
Director

TABLE VI*

Number of Treatments Given in the PMH Department of Radiotherapy
April 1984 — March 1985

EXTERNAL BEAM	
Superficial x-ray	1,856
Deep x-ray	3,136
Cobalt	41,210
Linear accelerators:	
Low energy	8,628
High energy	23,612
Betatron	4,921
TOTAL	83,363
Inpatient treatments	15,724
Outpatient treatments	67,639
TOTAL	83,363
SEALED SOURCES	
Intracavitary	251
Interstitial (needles, wires and seeds)	46
Strontium applicators	101
TOTAL	398

*Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1984-1985.

TABLE VII*

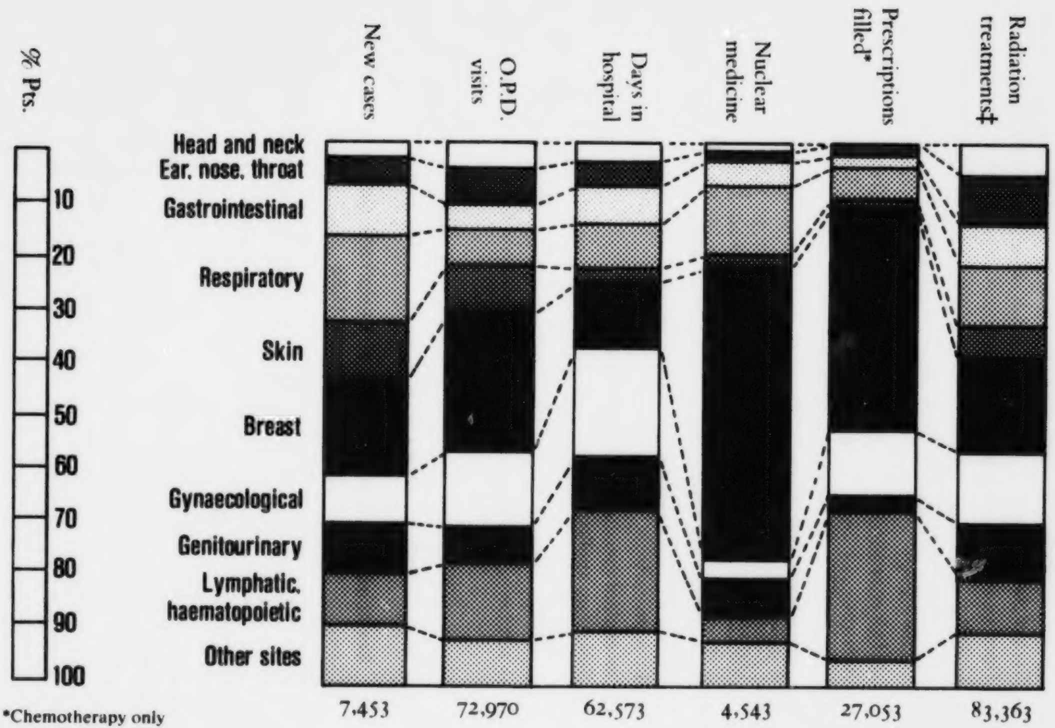
Services Provided by PMH at Peripheral Clinics
April 1984 — March 1985

CLINIC	NEW PATIENTS SEEN		PERIPHERAL CLINIC VISITS**	
	Malignant	Other	Malignant	Other
North Bay	135	19	1322	65
Owen Sound	89	3	732	15
Peterborough	38	1	1839	32
Sault Ste. Marie	34	0	746	11
Sudbury	17	1	1258	13
Timmins	34	7	1027	38
TOTAL†	347	31	6924	174

*Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1984-1985.

**Including the visits when patients are first seen at peripheral clinics as well as subsequent visits for new and old patients.

† In addition, 182 patients were registered at the Sudbury Oncology Clinic, as distinct from the Sudbury Peripheral Clinic, and seen by Dr. R. Corringham. They had a total of 2274 visits. Eighty-four of these patients are omitted from the other PMH (Ed.) tables because their records were not yet indexed.



*Chemotherapy only

‡External beam only

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Fig. 1. Princess Margaret Hospital workload by site of disease, expressed as a percentage of workload, April 1984-March 1985.

CONSULTATIVE AND FOLLOW-UP CLINICS

The distribution of these clinics reflects the general zones of service of the Foundation's Regional Cancer Centres in Hamilton, Kingston, London, Ottawa, Thunder Bay and Windsor; and of the Princess Margaret Hospital, Toronto.

HAMILTON
Brantford — St. Joseph's Hospital
Burlington — Joseph Brant Memorial Hospital
Cambridge (Galt) — Cambridge Memorial Hospital
Guelph — Guelph General Hospital
Hamilton — McMaster Medical Centre and St. Joseph's Hospital
St. Catharines — Hotel Dieu Hospital
Welland — Welland County General Hospital

KINGSTON
Trenton — Trenton Memorial Hospital

LONDON
Chatham — Public General Hospital
Kitchener — Kitchener-Waterloo Hospital
London — Victoria Hospital, Westminster Campus
Owen Sound — General and Marine Hospital
Sarnia — St. Joseph's Hospital and Sarnia General Hospital
Stratford — Stratford General Hospital
Wingham — Wingham and District Hospital
Woodstock — Woodstock General Hospital

OTTAWA
Cornwall — Cornwall General Hospital and Hotel Dieu Hospital
Pembroke — Pembroke Civic Hospital

THUNDER BAY
Fort Francis — Fort Frances Clinic
Geraldton — Geraldton District Hospital

TORONTO
North Bay — North Bay Civic Hospital
Owen Sound — General and Marine Hospital
Peterborough — St. Joseph's Hospital
Sault Ste. Marie — Plummer Memorial Public Hospital
Sudbury — Laurentian Hospital
Timmins — St. Mary's Hospital

WINDSOR
Leamington — Leamington District Memorial Hospital

CLINICAL CONSULTANTS AT THE OCTRF REGIONAL CANCER CENTRES AND THE PRINCESS MARGARET HOSPITAL

(As at December 31, 1985)

OCF Hamilton Centre:

M. Ali, M.D.
S. Archibald, M.D.
H.W. Beattie, M.D.
A.M. Benger, M.D.
W.F. Bennett, M.D.
I.W. Blackstone, M.D.
M. Brain, M.D.
P. Brown, M.D.
R.S. Bush, M.D.
A.J. Campbell-Moscrop, M.D.
B. Clark, M.D.
D. Clark, M.D.
J. Collins, M.D.
I.R. Davis, M.D.
P.B. Dent, M.D.
R. deVilliers, M.D.
B. Findlay, M.D.
J.D. Gowing, M.B.,B.S.
M. Gross, M.D.
R.A. Hadden, M.D.
J. Harvey, M.D.
A.A. Hitch, M.D.
G.K. Ingham, M.D.
B.S. Jackson, M.D.
P. Jenkin, M.D.
J. Kearns, M.D.
P. Knight, M.B.,Ch.B.
G.A. Lane, M.D.
E.J. Latimer, M.D.
J.A. McBride, M.B.,Ch.B.
R. Meyer, M.D.
W. Nicholson, M.B.,B.S.
S.E. O'Brien, M.D.
G.O'Connell, M.D.
W.L. Orovan, M.D.
M. Rathbone, M.D.
W.D. Rider, M.B.,Ch.B.
J.T. Roberts, M.B.,Ch.B.
D. Rosenthal, M.D.
D. Sauder, M.D.
D. Savelli, M.D.
B. Trossman, M.D.
P. Vasarinsh, M.D.
I. Walker, M.D.
W.E.C. Wilson, M.D.
C. Woolever, M.D.
J.E.M. Young, M.D.

OCF Kingston Centre:

J.M. Blakeman, M.D.
H. Brown, M.D.
J.A. Carmichael, M.D.
W.E.N. Corbett, M.D.
D. Dexter, M.D.
H.B. Dinsdale, M.D.
S.F. Hall, M.D.
J.W. Kerr, M.D.
K.W. Mackie, M.D.
R.J. Riopelle, M.D.
D.M. Robertson, M.D.
H.D. Steele, M.D.
E.E. Sterns, M.D.
K. Taguchi, M.D.
D.M.L. Williams, M.D.

OCF London Centre:

H.H. Allen, M.D.
D. Awde, D.D.S.
W.B. Barton, M.D.
R.M. Barr, M.D.
J. Chertkow, M.D.

J. Coles, M.D.
R.F. Del Maestro, M.D.
G. DeRose, M.D.
L.L. DeVeber, M.D.
A.A. Driedger, M.D.
J. Duff, M.D.
C.A. Dyson, M.D.
R. Finley, M.D.
K. Gay, M.D.
D. Girvan, M.D.
R.E. Greenway, M.D.
J. Harris, D.D.S.
H. Heeneman, M.D.
R.L. Holliday, M.D.
M.J. Inwood, M.D.
H. Lampe, M.D.
D. Macdonald, M.D.
D.A. MacKenzie, M.D.
J.A. McCredie, M.D.
R.M. McFarlane, M.D.
T.D. McLarty, M.D.
D.B. Meltzer, M.D.
D. Moulin, M.D.
J. Nisker, M.D.
M. Rock, M.D.
I.D.F. Schofield, D.D.S.
R. Shearer, M.D.
A. Smith, M.D.
M. Smout, M.D.
W.K. Stavraky, M.D.
J. Wyatt, M.D.

OCF Ottawa Centre:

D.J. Addison, M.B.,Ch.B.
G. Armstrong M.D.
E.A. Atack, M.D.
J.W. Atkinson, M.D.
G.G. Barber, M.D.
M.G. Bard, M.D.
R. Barr, M.B.,Ch.B.
P.T. Barron, M.B.,Ch.B.
A.W. Barry, M.D.
A. Baxter, M.B.,B.S.
P. Beaudry, M.D.
J.M. Belanger, M.D.
D.N. Bell, M.D.
M. Bell, M.D.
M.E.A. Bell, M.D.
B. Benoit, M.D.
P. Benoit, M.D.
J.M. Beresford, M.B.,Ch.B.
J. Bormanis, M.D.
A.G. Bouchard, M.D.
M.E. Bourke, M.D.
R. Boutin, M.D.
M. Brazeau, M.D.
B. Burns, M.D.
L. Busque, M.D.
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C.K. Chew, M.D.
G.C. Cimone, M.D.
J.C. Clark, M.D.
J. Collins, M.D.
J.M. Cowan, M.B.,Ch.B.
A. Crepeau, M.D.
H. Curry, M.D.
I. Dardick, M.D.
V. Da Silva, M.D.
Y. de la Bastide, L.R.C.P.(U.K.)
G. de la Salle, M.D.
J.J. Deneault, M.D.
J.P. Des Groseilliers, M.D.
J.E. Devitt, M.D.
C. Don, M.B.,B.S.
J. Drouin, M.D.
L. Eidus, M.D.
R.H. Elder, M.D.
C. Ellis, M.D.
R. Elliott, M.D.
R.J. Fairful-Smith, M.B.,Ch.B.
J.F. Fielding, M.D.
J.B. Freeman, M.D.
S.J. Fremeth, D.D.S.

S.W. French, M.D.
N.G. Futter, M.D.
L. Garnett, M.D.
E. Gear, M.D.
J. Gerin-Lajoie, M.D.
R.G. Gerridzen, M.D.
A. Giachino, M.D.
R.R. Gillies, M.D.
Z. Grahovac, M.D.
J.E. Green, M.D.
D. Grimes, M.D.
A. Guberman, M.D.
J.J. Hadju, D.D.S.
P. Hamilton, M.D.
A. Haq, M.D.
J. Hardie, B.D.S.
I. Hart, M.B.,Ch.B.
J. Henderson, M.B.,Ch.B.
R. Heringer, M.D.
A. Heron, M.D.
C. Hetenyi, M.D.
D.P. Hill, M.D.
R.B. Hladkowicz, M.D.
D. Hooper, M.D.
E. Hsu, M.D.
L.B. Huebsch, M.D.
H. Hugenholtz, M.D.
G. Hurteau, M.D.
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K. Kuwayti, M.D.
B. Lach, M.D.
G. Laframboise, M.D.
A. Lamothe, M.D.
J.E. Laws, M.D.
C. Leahy, M.D.
B.M. Lefebvre, M.D.
G.N. Lewis, M.D.
B.J. Lewandowski, M.D.
E. Liepa, M.D.
J.B. Lightford, D.D.S.
L. Lu-Godbout, M.D.
B. Luke, M.D.
P.C. MacEwen, M.D.
B.J. MacInnis, M.D.
J.P. MacLeod, M.D.
N. Mayer, M.D.
W.T.E. McCaughey, M.B.,Ch.B.
R.W. McIntyre, M.D.
W.M. McIntyre, M.D.
W.A. McLeish, M.D.
D.E. McKay, M.D.
J. McKenna, M.D.
N.V. McPhail, M.D.
S. Mehan, M.B.,Ch.B.
S. Mercer, M.D.
N.A. Mikhael, M.D.
D. Miller, M.D.
G. Mintsioulis, M.D.
V. Monpetit, M.D.
D. Moors, M.D.
J.E. Mullens, M.D.
J.P. Murnaghan, M.D.
R. Nelson, M.D.
K. Nolan, M.D.
P.F. Odell, M.D.
M. Orizaga, M.D.
H. Oxorn, M.D.
A. Peloquin, M.D.
E.W. Peterson, M.D.
R.A. Peterson, M.D.
J. Poliquin, M.D.
D.N. Preston, M.D.
D. Reid, M.D.
M.T. Richard, M.D.
R.N. Rivington, M.D.
J. Robblee, M.D.
N.A. Russell, M.D.
H.J. Sachs, M.D.
R. Saginur, M.D.
B. Samson, M.D.

G.J. Sarwer-Foner, M.D.
G. Sauve, M.D.
A.C. Scott, M.D.
J. Seely, M.D.
F.M. Shamji, M.D.
S.Y. Shirley, M.D.
M. Silverman, M.D.
D.S. Skene, M.D.
G. Skidmore, M.D.
R.K. Smiley, M.D.
H. Tao, M.D.
J.R. Taylor, M.D.
J. Thomas, M.D.
E.N. Thompson, M.D.
W.G. Thompson, M.D.
M. Tousignant, M.D.
B.K. Tsang, M.D.
G.N.W. Tse, M.D.
H.K. Uhthoff, M.D.
F.W. Vaillancourt, M.D.
C. Vezina, M.D.
V. Walley, M.D.
W.G. Walsh, M.D.
H. Warnes, M.D.
A.G. Watson, M.D.
C. Watters, M.D.
L. Weatherhead, M.D.
D.S. Whittingham, M.D.
K.B. Wilson, M.D.
R.W. Yarnell, M.D.

OCF Toronto-Bayview Centre:

D. Assaad, M.D.
B.D. Birt, M.B.,B.S.
P.L. Chan, M.D.
D.H. Cowan, M.D.
G.M. Davies, M.B.,B.Ch.
A.D. DePetrillo, M.D.
M. Fazl, M.D.
J.L. Freeman, M.D.
L. From, M.D.
J.S. Gruss, M.B.,B.Ch.
S. Hanna, M.B.,B.Ch.
A.W. Harrison, M.D.
S. Huang, M.D.
J. Hurwitz, M.D.
N.A. Kerenyi, M.D.
L. Klotz, M.D.
A. Kolin, M.D.
A.J. Lewis, M.D.
J.H.P. Main, D.D.S.
M.A. McKenzie, M.D.
H.A.B. Miller, M.B.,B.S.
E.R. Pohlman, M.D.,C.M.
B.P. Rosen, M.D.
D.W. Rowed, M.D.
M.L. Schwartz, M.D.
J.S. Senn, M.D.
J.R. Srigley, M.D.
G.A. Taylor, M.D.
M. Tile, M.D.
P.M. Webster, M.D.

The Princess Margaret Hospital Toronto

P.W. Alberti, M.B.,B.S.
U. Ambus, M.D.
J.D. Anderson, D.D.S.
A.G. Andrews, D.D.S.
A.G. Awad, M.D.
M.A. Baker, M.D.
J.L.M. Bean, M.D.
M. Berry, M.D.
N. Bharatwal, M.D.
M.E. Blackstein, M.D.
T.D.R. Briant, M.D.
A.W. Bruce, M.B.,Ch.B.
D.P. Bryce, M.D.
C.B. Bubela, M.D.
M.B. Buckspan, M.D.
M.L. Bunker, M.D.
G.N. Burrow, M.D.
J.J. Ceasar, M.D.
D.H. Carver, M.D.
H.S.L. Chan, M.B.,B.S.
A.W. Chisholm, M.D.

M.D. Christianson, M.D.
R.H. Comisarow, M.D.
J.G. Connolly, M.D.
J.D. Cooper, M.D.
D.H. Cowan, M.D.
J.S. Crawford, M.D.
A.D. DePetrillo, M.D.
L.G. Douglas, M.D.
W.M. Easterbrook, M.D.
R.J. Evans, M.D.
W.K. Evans, M.D.
R.E. Falk, M.D.
R.M. Filler, M.D.
E.B. Fish, M.D.
B.K. Fisher, M.D.
J.A. Fisher, M.D.
M.M. Fisher, M.D.
A.E. Franklin, Ph.D.
B.L. Gallie, M.D.
W.O. Geisler, M.D.
A.H. Gerulath, M.D.
R.J. Ginsberg, M.D.
C.M. Godfrey, M.D.
M. Goldberg, M.D.
S.D. Goldberg, M.D.
D.A. Gordon, M.D.
B.J. Green, M.B. Ch.B.
P. Gullane, M.B. B.Ch.
G. Haber, M.D.
J.A. Hakes, M.B. Ch.B.
M.L. Halperin, M.D.
W.J. Hannah, M.D.
G.D. Hart, M.D.
D.E. Hastings, M.D.
R.I. Hector, M.D.
C. Hegarty, M.B. B.Ch.
M.E. Hill, M.D.
M.S. Hill, L.R.C.P.
C.H. Hollenberg, M.D.
R. Hopkins, D.D.S.
N.S. Hradsky, M.D.
R.C. Hunter, M.D.
M.A. Hutcheon, M.D.
R.H. Hyland, M.D.
C.G. Jamieson, M.B. B.S.
R.D.T. Jenkin, M.B. B.S.
S.E. Jelenich, M.D.
M.A. Jewett, M.D.
D.W. Jirsch, M.D.
D.P. Jones, M.D.
A.T. Jousse, M.D.
A.S. Katz, M.D.
A. Keresteci, M.D.
W.K. Kerr, M.D.
M.H. King, M.D.
G.H. Knutson, M.D.
B. Langer, M.D.
F. Langer, M.D.
V.G. Lawson, M.D.
W.D. Leers, M.D.
G.M. Lickrish, M.B. Ch.B.
F.H. Lowy, M.D.
W.J.C. MacArthur, M.D.
R.D. MacDonald, M.D.
I.M. MacKay, M.D.
T.A. MacKenzie, M.D.
I. Macnab, M.B. Ch.B.
L.J. Mahoney, M.D.
J.H.P. Main, D.D.S.
N.E. Marcon, M.D.
J.T. Matorra, M.D.
A.G. Matlow, M.D.
W.G. Maxymiw, D.D.S.
P.H. McCleary, M.D.
J.S. McGrail, M.D.
J.W. Meakin, M.D.
T.J. Molony, L.R.C.P.(U.K.)
C.B. Mortimer, M.D.
P.J. Muller, M.D.
T.M. Murray, M.D.
R.E. Myers, M.D.
J.R. Nethercott, M.D.
R.J. Osborne, M.D.
D. Osoba, M.D.
F.R. Papsin, M.D.
G.A. Patterson, M.D.

F.G. Pearson, M.D.
R.G. Perrin, M.D.
D.G. Potts, M.D.
K. Pritchard, M.D.
P. Ramachandran, M.D.
C.A. Ramsay, M.D.
J.T. Rankin, B.M.,B.Ch.
I.B. Rosen, M.D.
L. Rotstein, M.D.
R.K. Schachter, M.D.
J. Schatzker, M.D.
A.A. Scott, M.D.
M. Scott, M.D.
J.S. Senn, M.D.
M. Silberfeld, M.D.
M.D. Silver, M.D.
E.R. Simpson, M.D.
G. Foster Smith, M.D.
H.S. Smyth, M.D.
H.A. Smythe, M.D.
M.J. Sonley, M.D.
M.L. Soots, M.D.
A.H. Squires, M.D.
R.M. Stone, M.D.
P. Straka, M.B.,Ch.B.
D.J. Sutherland, M.D.
J.D. Swales, M.D.
J.M. Symington, B.D.S.
S.A.P. Tindal, M.B.,Ch.B.
J. Trachtenberg, M.D.
M.L.S. Vachon, Ph.D.
C.P. Vernon, M.D.
R. Volpe, M.D.
C.P.N. Watson, M.D.
N.A. Watters, M.D.
G.D. Webb, M.D.
R.H. Wilkinson, M.D.
C.C. Williams, M.D.
F.R.H. Wrigley, M.B.,B.S.
A. Zipursky, M.D.
R.M. Zuker, M.D.

SPECIAL SERVICES

PROVISION OF SPECIAL DRUGS TO TREAT MALIGNANT DISEASE

The Foundation provides special chemotherapeutic agents to cancer patients who are residents of Ontario and are at home under the care of their doctors. This program was undertaken to assist those patients who find the cost of prolonged therapy with expensive drugs beyond their financial resources.

The total cost of the drug service in 1984 was $572,300.25 -- an increase of 27% from the $450,872.94 in the previous year (Table I). In 1984, 9,212 prescriptions were filled and the cost per prescription has increased to $62.86 from $48.94 in 1983.

TABLE I

Cost of Drug Service 1975-1984

Year	Payments for Drugs	Total Cost of Drug Service
1975	214,942.30	216,055.35
1976	175,949.99	177,984.37
1977	148,418.40	152,021.06
1978	209,817.12	210,836.18
1979	257,136.92	261,512.36
1980	259,973.32	265,059.36
1981	307,376.30	307,676.97
1982	370,388.28	375,971.20
1983	448,401.93	450,872.94
1984	569,966.52	572,300.25

CARCINOEMBRYONIC ANTIGEN (CEA) AND STEROID-RECEPTOR ASSAYS PROGRAM

The Ontario Cancer Treatment and Research Foundation is administering and monitoring a program for carcinoembryonic antigen (CEA) and steroid-receptor assays which is funded by the Ministry of Health. The CEA assays for confirmed cases of cancer and the steroid-receptor assays for confirmed cases of breast carcinoma are available, at no charge, to a patient when these assays are performed in the designated laboratories listed below.

During the fiscal period April 1, 1984 to March 31, 1985, 4,393 steroid-receptor assays and 42,137 CEA assays have been performed in the designated laboratories.

All laboratories in Ontario are familiar with the program and can provide the details of the data required, sample requirements and specimen transportation. Specimens can be referred to the participating laboratories listed below either directly or through the laboratory which usually provides such services.

Laboratories in the CEA-Assay Program

McMaster University Medical Centre — Dr. E.D. Ryan
1200 Main Street West
Hamilton, Ontario L8S 4J9 tel: (416)525-9140

Kingston General Hospital — Dr. A.F. Clark
Stuart Street
Kingston, Ontario K7L 2V7 tel: (613)547-2121

Victoria Hospital — Dr. E.R. Tustanoff
375 South Street
London, Ontario N6A 4G5 tel: (519)432-5241

Ottawa Civic Hospital — Dr. C. Lapkoff
1053 Carling Avenue
Ottawa, Ontario K1Y 4E9 tel: (613)729-2511

General Hospital of Port Arthur — Dr. N. Escott
460 North Court Street
Thunder Bay, Ontario P7A 4X6 tel: (807)344-6621

Sunnybrook Medical Centre — Dr. A. Malkin
2075 Bayview Avenue
Toronto, Ontario M4N 3M5 tel: (416)486-3626

Laboratories in the Steroid-Receptor-Assay Program

McMaster University Medical Centre 1200 Main Street West Hamilton, Ontario L8S 4J9 tel: (416)525-9140	Dr. E.D. Ryan
Victoria Hospital 375 South Street London, Ontario N6A 4G5 tel: (519)432-5241	Dr. E.R. Tustanoff
Ottawa Civic Hospital 1053 Carling Avenue Ottawa, Ontario K1Y 4E9 tel: (613)729-2511	Dr. T. Ooi
Sunnybrook Medical Centre 2075 Bayview Avenue Toronto, Ontario M4N 3M5 tel: (416)487-2722	Dr. D.J.A. Sutherland
University of Toronto Medical Sciences Bldg., Rm. 7336 Toronto, Ontario M5S 1A8 tel: (416)978-3553	Dr. G.E. Mobbs

DIAGNOSTIC BIOPSY SERVICE AND VOLUNTARY REPORTING BY PATHOLOGISTS

The diagnostic biopsy service was established by the Foundation to pay for biopsies on uninsured patients. In 1984, 5420 specimens were submitted by dentists (4676 in 1983).

The number of reports voluntarily submitted by the directors of pathology departments has continued to increase and, in 1984, 51,644 reports were submitted, a 5% increase over the 47,560 reports submitted in 1983.

These reports are used in the generation of cancer incidence data for Ontario and are most valuable in confirming the diagnosis of new cases. The Cancer Act, R.S.O. 1980, Chapter 57, Section 4, Item 7, provides protection for physicians, dentists and hospitals reporting information on cancer incidence to the Foundation. The information from the reports is used for epidemiological and statistical purposes only.

The Foundation gratefully acknowledges the continuing co-operation of the participating pathologists and hospitals, and the support of the Ontario Association of Pathologists in the acquisition of these data.

LODGES FOR AMBULATORY CANCER PATIENTS

At present, the Foundation administers and funds the operation of five lodges for out-of-town ambulatory cancer patients attending the regional cancer centres for diagnosis and treatment. These lodges provide comfortable, supportive accommodation, with minimal supervision, at no cost to the patient. Escorts are accommodated at minimal cost when beds are available.

The Foundation provides this accommodation because location of the treatment centres often requires the patient to travel a considerable distance; without these facilities, the patient would require hospitalization at far greater expense to the Province.

The table below shows the current facilities, the number of beds and the patient days spent in each lodge during the fiscal year ended March 31, 1985.

		Number of Beds	Patient Days
KINGSTON	– Quinte-Thousand Islands Lodge	26	4,634
LONDON	– Thameswood Lodge	50	9,501
OTTAWA	– Maurice J. Grimes Lodge	36	7,731
THUNDER BAY	– Amethyst House Lodge	18	2,205
TORONTO	– Princess Margaret Hospital Lodge	105	22,849

Patients who require hostel accommodation while being treated at the Toronto-Bayview Regional Cancer Centre are housed in facilities offered, on a temporary arrangement, by Sunnybrook Medical Centre; 1,495 patient days were recorded in this fiscal year.

Construction of the new Lakeview Lodge in Hamilton was completed in November 1985. This facility, which currently provides 20 beds, will be officially opened on April 22, 1986.

TRANSPORTATION OF CANCER PATIENTS

The Foundation covers the cost of transportation to any one of its regional cancer centres or to the Princess Margaret Hospital of those patients who live more than 25 miles from the centre and are considered to be in financial need. For patients 18 years or less, transportation is provided to the principal pediatric oncology treatment centres in the five health science complexes, namely:

HAMILTON — McMaster Medical Centre
KINGSTON — Kingston General and Hotel Dieu Hospitals
LONDON — War Memorial Children's Hospital,
Victoria Hospital Corporation
OTTAWA — Children's Hospital of Eastern Ontario
TORONTO — Hospital for Sick Children

Usually transportation is arranged by the local unit of the Canadian Cancer Society, which subsequently is reimbursed by the Foundation.

For the fiscal year ended March 31, 1985, the total cost for transportation of patients was $658,205, compared to $478,815 for the fiscal year ended March 31, 1984.

CANCER INFORMATION SERVICE

The Cancer Information Service, a pilot project, is funded by the Ontario Cancer Treatment and Research Foundation and the Canadian Cancer Society Ontario Division.

In April 1985, this toll-free telephone service began to provide the most up-to-date factual information on cancer and cancer-related resources to the general public, cancer patients and their families, health professionals, and the media.

The service is staffed by health professionals and carefully trained volunteers who respond to calls using information of varying complexity. This ranges from simple pamphlets prepared by the Canadian Cancer Society, through nursing and medical texts and articles, to the Physician Data Query (PDQ) system -- a computerized data base. PDQ, which was developed by the National Cancer Institute and is updated monthly, provides professionals with the most comprehensive information on cancer treatment including current research protocols.

To date we have received approximately 1900 calls. Forty per cent of calls come from spouse, other relatives, or friends of the patient, 17% from patients, 17% from the general public and 27% from others.

The sites most commonly mentioned by those who call parallel the frequency in the general population. Breast and respiratory tract are the most frequent, followed by cancers of the genito-urinary tract, the digestive tract, leukemias and lymphomas.

Among those who call, females outnumber males by 4:1. Approximately 20% are repeat users. Questions are received from all age groups. Most callers (over 65%) have high-school education or better.

Many callers indicate that they believe the service is valuable because it was the only place they had been able to obtain comprehensive information regarding the subject of their concern.

In the second year of service, we hope to increase the overall use of the service, especially its use by professionals.

Calls are answered Monday to Friday, between the hours 9:00 and 17:00.

RESEARCH PROGRAMS

SUMMARY OF OCTRF RESEARCH

Over the past few years, the Foundation has done a careful review of its research priorities in light of current fiscal constraints. As a result, as its top priority, it identified the support of career scientists working in the regional cancer centres, the senior scientific staff at the Ontario Cancer Institute, and support of research associates/scholars in the health sciences complexes. To accomplish these goals, the grants-in-aid program was terminated in 1982, and funding for projects previously supported was terminated on March 31, 1985.

In addition to these scientists, the Foundation also supports the Research Unit of the OCTRF located in the Department of Preventive Medicine and Biostatistics at the University of Toronto, and clinicians and physicists in the regional cancer centres who participate in research part-time.

A major new component of the Foundation's research program is the Ontario Clinical Oncology Group, which was established in 1983 through an award of $500,000, made by the Ministry of Health, from lottery funds. Two trials activated in the past two years already have accrued over 500 patients and three additional trials are in the planning stages.

Career Scientists Program

The Subcommittee on Support of Research Personnel is charged with the task of recommending the appointment of young career investigators to the Foundation's regional cancer centres and their reappointment. During the past two and one half years, it has recommended the appointment of eight new career scientists. There are now two career scientists at the Hamilton Centre, three in Kingston, four in London, and two in Ottawa. Eventually the Foundation hopes to support at least 20 career scientists – four in each of the university-affiliated centres. In addition to salary support, the Foundation also provides "start-up" funds for essential equipment and supplies. If necessary, it will provide limited operating funds for up to two years if the scientist cannot obtain peer-reviewed support through external granting agencies. Requisites for reappointment include the maintenance of peer-reviewed grant support, publications in peer-reviewed journals and periodic review of their research endeavors, either from the Centre's director or the dean of the affiliated university or site review. We are happy to report that all 11 career scientists have obtained peer-reviewed grant support for the 1985/86 year despite keen competition. This success reflects the high calibre of the scientists who work in our Centres. We congratulate them on this major accomplishment and wish them every success in the 1986/87 competitions.

Research Associates/Scholars

For many years the Foundation provided salary support for research associates working in various health sciences centres throughout the Province. These were "life appointments", dependent upon the maintenance of peer-reviewed grant support, publications in peer-reviewed journals and periodic site review. At the present time the Foundation supports seven research associates.

In an effort to involve young scientists in cancer research, the Subcommittee recommended that the research associate program be eliminated, with the understanding that support of current research associates would continue in accordance with their original appointment. In addition, a new research scholar program was established, which provides salary support for five years, once renewable. This renewal is subject to the same criteria as that of the research associates.

The first OCTRF Research Scholarship Competition was held in October 1983 and one scholar was appointed, effective July 1, 1984. A second competition was held in October 1984. The Subcommittee recommended and the Board approved two more scholarships. These appointments became effective on July 1, 1985. Unfortunately, the first of these new scholars terminated his scholarship on October 15 and returned to the U.S.A.

Because of financial constraints a scholarship competition was not held in 1985. All hope that a third competition will be held in October 1986.

Senior Scientific Staff at the Ontario Cancer Institute

The Foundation provides an annual block grant to the Ontario Cancer Institute to provide salary support for the senior scientific staff of its Divisions of Biology and Physics. This grant includes limited funds for equipment, supplies, travel, etc. Further on in this section we append a brief resume of some of the research being pursued at the Ontario Cancer Institute. The Institute's 1984-85 Annual Report outlined the research and other achievements of members of their Divisions of Biology and Physics. Some of these can be summerized as follows.

Electron Microscope. After more than 15 years of research, an electron microscope developed at the OCI/PMH, by Dr. Peter Ottensmeyer, is now being commercially manufactured for use in research and clinical laboratories around the world. The new microscope provides a much clearer and sharper image, and even can identify the type and location of individual atoms. The OCI/PMH entered into an agreement with Carl Zeiss of West Germany to produce a commercial version, and Zeiss presented the first production model of the EM902 to the OCI/PMH Pathology Department to assist them in the diagnosis of cancer.

Magnetic Resonance Imaging. The OCI/PMH was fortunate to be selected by the Ministry of Health as the first centre in Ontario to receive the prototype magnetic resonance imaging (MRI) machine for research. MRI produces an image similar to a CT scan, but does not use x-rays or any form of radioactivity. Research at OCI has focussed on the use of MRI in detecting cancer in soft tissue. However, MRI is now considered the best imaging method available for the base of the brain and the spine. Bone interferes with most imaging techniques, but to MRI bone is invisible.

Scanning with Ultrasound. With the help of physicians at the Princess Margaret Hospital and the Women's College Hospital, the ultrasound team is evaluating the ability of this scanner to detect abnormalities of the breast. More than 950 women have been examined using both the new ultrasound and traditional x-ray mammography. So far, it appears that ultrasound has unique abilities in young patients with dense breasts, while the x-ray mammography is more accurate for patients with fatty breasts. However, the two systems complement each other.

Cancer Cells Resistance to Drugs. Dr. Victor Ling has discovered that a certain protein (p-glycoprotein) was increased quantitatively on the surfaces of cancer cells resistant to a variety of chemotherapeutic agents. He has provided evidence that cells may become resistant by increasing their p-glycoprotein production. This observation raises the possibility that different but related p-glycoproteins may be involved in generating the complex multi-drug resistance of cancer cells.

T-Cell Receptors. Two years ago, Dr. Tak Mak and his research team were the first to isolate a molecular clone for the beta-chain of the receptor on T lymphocytes. Since then Dr. Mak has exploited and extended his observations. He has provided proof for the hypothesis that the T-cell receptor is an alpha-beta heterodimer and that the molecular clones encode for it.

The Gene Machine. The OCI has obtained two machines which build chains of nucleotides or amino acids in specified order. With such facilities, scientists at the Institute will be able to prepare artificial genes to compare the genetic compositions of normal and cancerous cells.

OCTRF Core Grants

In addition to providing salary support, "start-up" funds and operating funds, if necessary, the Foundation provides an annual award to cover the uncommon needs of career scientists in the regional cancer centres. These funds cover expenditures for secretarial support, travel costs for the investigator(s) or guest speakers, service contracts, etc., that usually are not provided through operating grants.

Clinicians/Physicists Involved in Research

Although the Foundation does not provide direct research funding, a number of the Centres' clinicians and/or physicists are involved in part-time research. Members of the Centres also participate in clinical trials, either on a single-centre basis, in collaboration with other centres, and/or with national or international groups.

Research Unit of the OCTRF

Members of the Foundation's Division of Epidemiology and Statistics participate in research and obtain operating funds through peer-reviewed grant support from external granting agencies.

Since 1978, the Research Unit has been affiliated with the Department of Preventive Medicine and Biostatistics, University of Toronto. The Unit was established to conduct analyses using the cancer data bases of the OCTRF to assess the quality of these data, to co-operate with cancer researchers by providing epidemiological and biostatistical assistance, to conduct or support cancer research projects, and to provide information to the scientific community and the general public.

Grants-in-Aid Program

As noted previously, the grants-in-aid program was terminated on March 31, 1985. However, final results of some of the projects will not be available for some time because of the long follow-up period needed before analyses can be completed.

The Research Programs section includes reports on the research programs pursued by the career scientists, research associates, research scholars and staff of the regional cancer centres, members of the Ontario Cancer Institute and the Foundation's Research Unit. Progress and/or final reports for some of the research projects funded in the past also are included in this section.

Appendix B lists publications by personnel supported by the Foundation and publications relating to projects it previously funded.

Ad Hoc Cancer Research Advisory Committee

At the request of the Foundation Board, and in collaboration with the Health Research and Development Council of Ontario, the Ad Hoc Cancer Research Advisory Committee was established in February 1985 to review cancer research programs in Ontario as a whole, taking into consideration the views of the Foundation centres, the Ontario Cancer Institute, and the health sciences complexes. This committee was asked to make recommendations about future cancer research needs, priorities, structures and co-ordination.

The committee of eight members had representatives from the Foundation regional cancer centres, the Ontario Cancer Institute, the health sciences complexes, and the Health Research and Development Council of Ontario. The committee, with Dr. J.E. Till as chairman, met for the first time early in March and worked until early July when they submitted their report to Dr. J.W. Meakin for presentation to the Board. In September 1985, this document was presented to the Board and to the acting director of the Health Research and Development Council of Ontario for their consideration.

In undertaking this onerous task, the committee concentrated on six specific areas of research, namely: epidemiology and prevention; early detection and screening; basic and clinical research; quality of life; and health services research.

As a result of their deliberations, the committee made 19 specific recommendations. One of the most significant was that the Research Committee, as currently constituted, be replaced by a small Research Advisory Panel, comprised of a chairperson and six members representing the Foundation Centres, the Ontario Cancer Institute, and the health sciences complexes.

The Board approved the report in principle on December 9, 1985. The terms of reference and membership for a research advisory panel were approved with some minor modifications. The Board also recommended that when this panel is established, it considers Recommendations 1 to 18 of the Report of the Ad Hoc Cancer Research Advisory Committee and reports back at the earliest opportunity.

Mary Parkes
Research Assistant

The Ontario Clinical Oncology Group

Between March and June of 1984, the group initiated two Phase III trials. Each compares two different treatments in the two most common stages of female breast cancer. The first trial compares conservative surgery (lumpectomy) alone with lumpectomy followed by adjuvant radiotherapy to the effected breast in Stage I breast cancer (small primary tumor in the breast and pathologically negative axillary nodes). By August 30, 1985, 200 patients had been entered in the trial from the participating regional cancer centres -- Hamilton, Ottawa, Thunder Bay, and Windsor -- and in Toronto the Princess Margaret Hospital. The second trial compares a short (three months) intensive adjuvant chemohormonal therapy with a longer (nine months) less intensive therapy as an adjuvant in Stage II breast cancer (primary tumor removed from the breast, and some axillary nodes pathologically positive for metastatic disease but with no evindence of systemic cancer). By August 30, 1985, 198 patients had been entered from the participating regional cancer centres from Hamilton, London, and Thunder Bay.

These trials continue to accrue patients at an increasing rate. A team consisting of the principle investigator and members of the data centre (at McMaster University) travelled to each local centre at the start of the trial. Also the sponsors carry out continuing on-site visits and participant conferences every few months. These measures have maintained a high level of enthusiasm among local investigators and the support staff -- clinical trials' nurses, secretaries, etc.

To upgrade the qualifications of clinical investigators within the Province, a three-day workshop was held in mid-April 1985 at the McMaster University, Department of Clinical Epidemiology and Biostatistics. The 21 participants represented medical and radiation oncology from all seven OCTRF regional cancer centres, the Ontario Cancer Institute, and the University of Toronto. The participants were divided into three tutorial groups. Twelve members from McMaster University acted as plenary session lecturers and tutors for the groups. The participants were supplied with an abundance of self-learning material beforehand, instruction during the plenary sessions, and coaching in tutorial groups.

At the end of the workshop, each of the groups presented well-thought-out, preliminary, clinical trial proposals, which they developed during the tutorial sessions. Six topics were identified and discussed during the workshop: The research question; design and architecture; selecting the sample and defining the maneuver; outcome and measurement; sample size and statistical analysis; and ethical considerations. The verbal and written feedback received during and following the workshop demonstrated that it was an uniformly excellent educational experience.

In late 1984 and early 1985, approximately 15 new draft proposals were received and evaluated by the policy committee. As instructed, the co-ordinator proceeded to investigate one of the proposals and began to plan for two further trials. The centre's staff hopes to define the magnitude of the problem of spinal-cord compression by a search of the records at the Hamilton and London Centres. The sponsors may prepare an educational package for the medical profession and for cancer patients as part of a paraplegia prevention clinical trial. All oncologists are aware that this disastrous complication may produce sudden paraplegia in patients whose systemic malignancy otherwise may be well controlled. However, a literature search and an examination of data in the Ontario Cancer Registry do not, as yet, delineate the precise magnitude of this problem. When the size of the groups at risk with various cancer diagnoses has been determined in typicl patient populations attending Ontario cancer centres, it may be possible to devise a clinical trial of early detection and prevention of paraplegia.

We continue to meet with interested co-ordinators of gynecologic oncology from Toronto, Hamilton and London, and with radiation therapists, medical oncologists, and members of the methodology centre to define a Phase III trial in locally advanced, surgically resectable, endometrial carcinoma. This trial would compare two types of radiation and attempt to define the adjuvant role of progestational agents in this group of patients. In locally advanced, squamous-cell carcinoma of the head and neck, we have circulated a draft protocol to compare conventional surgery and/or radiation with curative intent. A conventional (surgery and/or radiation) arm would be compared to neoadjuvant chemotherapy followed by defintive radiationa and/or surgery to determine the potential for increased relapse-free survival. Physicians from Hamilton, Kingston, London, Ottawa, Toronto-Bayview, Windsor, and the Princess Margaret Hospital have expressed sufficient interest in this design that they have sought approval for such a trial from their local head and neck specialty groups.

One-half of head and neck cancer patients present with disabling local symptoms which require either palliative or curative treatment. Initial treatment is often successful, but many will relapse within one year and suffer a prolonged illness because the disease tends to spread locally rather than distantly. Extensive medical and social support is required. A program which substantially reduces the relapse rate would alleviate personal suffering and reduce the cost of services required to support individual patients and families.

The two ongoing studies in breast, and the studies previously proposed, all use tools to evaluate and compare quality of life as well as direct cost to the health care system and to the patient -- time lost from work, travel cost, child and other dependent care costs, etc.

Past and proposed budgets for this group demonstrate the wisdom of our decision to use the initial provincial lottery grant as seed money to promote multicentre clinical trials in the Province, to increase the number of potential investigators and the quality of proposed investigative protocols, and to develop selected protocols to the point where funding can be sought from external (national or international) sources.

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Program Co-ordinator

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McMaster University, Hamilton

IMMUNOBIOLOGY OF A MELANOMA-ASSOCIATED ANTIGEN DEFINED BY MONOCLONAL ANTIBODIES*

S.-K. LIAO**, *Hamilton, Ontario*

We have been characterizing surface antigens of human melanoma cells to determine if some of these antigens can be used for studies in tumor biology and to aid in the development of tumor phenotyping and therapeutic reagents.

The hybridoma technique by which monoclonal antibodies can be obtained provides a powerful tool to identify antigens expressed strongly, if not exclusively, on tumor cells. We have studied extensively one such antibody which has been raised against melanoma cells. This antibody, designated 140.240, detects an epitope of a 87K dalton glycoprotein (gp87), which is expressed strongly by both cultured and fresh melanoma cells as well as by fetal intestine. However, this molecule is expressed weakly by normal melanocytes grown in medium containing a tumor promoter, TPA, and cholera toxin. Removal of TPA from the culture medium significantly decreases the cell growth with a concomitant decrease in the synthesis and expression of gp87. Studies are underway to determine if gp87 can substitute for TPA as an autocrine growth factor for melanocyte growth.

One of the biological functions of gp87 is iron binding, acting as a member of the transferrin family. While we know nothing about the importance of gp87 in iron regulation as compared with the transferrin/transferrin receptor system for melanoma-cell proliferation, it offers an opportunity to study this tissue-associated and growth-related molecule in the melanocytic-cell lineage.

We also have produced a second generation of monoclonal antibodies to gp87 purified by antibody-affinity chromatography. The epitopes recognized by six such monoclonals are different from one another and from that recognized by 140.240. We have demonstrated different serological specificities resulting from antibody recognition of the same molecule (gp87)/different epitopes; this suggests that it is important to conduct a detailed serological assay to identify the best epitope specificity of different antibodies to a single tumor-associated antigen. We are aiming at selection and use of a combination of these monoclonal antibodies in the quantitation of the antigen in circulation, and in tumor imaging and radioimmunotherapy.

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*RA-204.

**Associate Professor of Pathology, and of Pediatrics, McMaster University, Hamilton; and OCTRF Research Associate, Hamilton Regional Cancer Centre.

This project was supported by a grant (MA-5637) from the Medical Research Council of Canada.

ABSORPTION AND METABOLISM OF EQUINE ESTROGENS IN NORMAL MEN AND POSTMENOPAUSAL WOMEN*

B.R. BHAVNANI** and C.A. WOOLEVER**, *Hamilton, Ontario*

Conjugated equine estrogens are used widely for replacement therapy in postmenopausal women and, recently, these estrogens have been implicated in the genesis of carcinoma of the endometrium. We have demonstrated that in postmenopausal women equilin sulfate -- one of the main components of conjugated equine estrogen preparations, is metabolised to equilin[1]. In normal men[2] and in postmenopausal women[3], equilin sulfate and equilin are further metabolised to 17β-dihydroequilin and 17β-dihydroequilin sulfate. 17β-dihydroequilin is 4 to 8 times more potent as a uterotropic agent than estradiol and equilin respectively. To continue this work we are investigating the metabolic fate of 17β-dihydroequilin in postmenopausal women.

To determine the plasma levels of 17β-dihydroequilin in postmenopausal women taking conjugated equine estrogens we are developing a radioimmunoassay for 17β-dihydroequilin. To date we have synthesized high-specific-activity 2,4,^{3}H-17β-dihydroequilin and its sulfate for use in the development of radioimmunoassay procedures, in a manner similar to that we described for equilin[1]. Because our preliminary results indicated that the antiserum used for equilin assay was not suitable for the assay of 17β-dihydroequilin, we have started to raise antibodies against 17β-dihydroequilin, by immunizing rabbits with 17β-dihydroequilin-17βHSA. This human serum albumin (HSA) steroid complex was synthesized via the 17-hemisuccinate and final coupling with HSA by carbodimide condensation reaction. The purified steroid protein complex was emulsified in Freund's adjuvant and was injected subcutanously at several different sites on the back. At present the titers of the antiserum are not high enough for the radioimmunoassay of 17β-dihydroequilin. Once the appropriate antiserum is available we will continue the development of the assay. The 17β-dihydroequilin sulfate will be assayed after solvolysis of the plasma.

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*Project 388. (Final Report)

**Professor of Obstetrics and Gynecology, McMaster University, Hamilton.

CHEMOTACTIC INHIBITORS IN CANCER*

L.A. MANDELL**, *Hamilton, Ontario*

Chemotaxis refers to the directed migration of neutrophils toward a site of inflammation -- a movement that is regulated by both stimulatory and inhibitory mechanisms. It has been reported that chemotactic inhibitors, which are present in normal serum in minute concentrations, are increased in several diseases. Our purpose is to demonstrate such inhibitors in the serum of cancer patients and to characterize their specificity and mechanisms of action. The functional definition of these inhibitors is essential to a more complete understanding of the inflammatory process and to our comprehension of the cancer patient as an immunocompromised host.

A standard method is used to measure chemotaxis with C5a and bacterial filtrate (BF) as the chemoattractants. Serum from 81 patients with various tumors at different stages of progression were tested to determine the presence of chemotactic-factor inhibitors (CFI) or cell-directed inhibitors (CDI). In addition, preliminary tests have been done on lysates from tumor cells grown in cell culture. All results were analyzed statistically.

Patients with lung cancer and leukemia had inhbitors of chemotaxis due to CFI directed against the chemoattractant C5a but not BF. Lymphoma patients showed CFI directed against both C5a and BF. Chemotactic inhibition, due to CDI specific for C5a (as the attractant), was noted in association with lung cancer but CDI with both BF and C5a were found with leukemia and lymphoma. No CDI were detected with breast cancer. Lysates of T- and B-cell lymphomas grown in tissue culture demonstrated both CFI and CDI activity.

A morphometric analysis of inhibited and control neutrophils, using scanning electron micrographs, showed a significant alteration in shape of the inhibited cells.

The results indicate that both type and specificity of chemotactic inhibitor depend upon the underlying tumor. A greater heterogeneity of inhibitors was found than had been previously suspected.

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*Project 438.

**Head, Division of Infectious Diseases, McMaster University, Hamilton.

Hamilton Regional Cancer Centre

IN VITRO BIOLOGICAL STUDIES OF PHOTODYNAMIC THERAPY USING A MULTICELL SPHEROID MODEL*

W.P. JEEVES**, *Hamilton, Ontario*

Basic and clinical studies have demonstrated that photodynamic therapy (PDT) constitutes a significant advance in our ability to eradicate or control a variety of localized tumors[1]. In PDT, the tumor is irradiated with high-intensity visible light after intravenous administration of the photosensitizing hematoporphyrin derivative (HPD). However, we know relatively little about how tumor response to PDT can be modified by changing treatment variables, or how the efficiency of tumor cell killing is affected by variations in oxygen and nutrient concentration within solid tumors.

We are using multicell spheroid cultures of the V79 Chinese hamster cell line to study the uptake kinetics and distribution of HPD, by either fluorescence flow cytometry, or by radioassay of spheroids incubated with radiolabelled drug. Preliminary results suggest that the uptake of HPD into spheroids may be diffusion-limited[2], and current experiments will test the possibility that a gradient of HPD may exist throughout the spheroid volume.

An irradiation chamber has been constructed, which allows spheroids to be exposed to light under strictly controlled conditions while they are in spinner culture. Early results indicate that while neither HPD nor light alone produces a significant effect on spheroid cell killing, treatment with HPD plus light results in a marked reduction in spheroid colony-forming ability, which is drug-concentration and light-dose dependent[2]. This chamber will be used for detailed studies of spheroid-cell killing as a function of HPD concentration and light dose/dose rate, and of factors such as temperature and oxygen tension before, during, and after irradiation. Knowledge of the effects of these parameters will assist in the development and refinement of treatment protocols, and thus promises to improve results of clinical treatment.

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*CS-105.

**Career Scientist, OCTRF Hamilton Regional Cancer Centre; and Assistant Professor of Pathology, McMaster University, Hamilton.

MITOCHONDRIAL DNA AS A CRITICAL TARGET FOR TOXICITY CAUSED BY ANTINEOPLASTIC DRUGS*

G. SINGH**, *Hamilton, Ontario*

The utility of most cancer chemotherapeutic agents is limited by their toxicity. Further, the mechanisms underlying the specific organ toxicities remain unclear. Traditionally, investigators have focussed on nuclear DNA, or plasma membrane, or cytoplasmic proteins as targets of reactive moieties generated from chemotherapeutic agents and other cytotoxic chemicals.

This study is based on the hypothesis that mitochondrial DNA may be a critical target of cytotoxic drugs, especially some used in cancer treatment. The rationale for postulating such a hypothesis are: (a) preferential binding of certain compounds to mtDNA compared to nuclear DNA; (b) accumulation of several drugs by mitochondria; (c) morphological evidence suggesting mitochondrial damage; (d) the poor mitochondrial DNA repair processes compared to nuclear DNA repair; and (e) the lack of "protective" histones on mitochondrial DNA.

The short-term goal of this proposal is to investigate whether mitochondrial DNA is a critical target for nephrotoxicity induced by cisplatin using the mouse as a model system. To investigate this possibility, the study will determine the effect of cisplatin, transplatin and other platin analogues that do not cause nephrotoxicity on: (i) a product of the mitochondrial genome, i.e., catalytic subunit of cytochrome oxidase – translation product of mtDNA; (ii) the mitochondrial genome itself – examination for mtDNA damage; (iii) changes in mitochondrial morphology as a function of time and dose -- using electron microscopy; (iv) mitochondrial electrochemical gradient as an index of mitochondrial function; and (v) oxidative phosphorylation also a determinant of mitochondrial intactness.

I have developed a reliable method of studying damage in mitochondrial DNA using both cell culture and cell-free systems[1]. This method insures specificity to the intracellular DNA target being assayed. The radiolabelled probe is crucial to the procedure because it provides both a means of quantitation by radioautography and a means to obtain the mtDNA specificity required to eliminate artifacts due to contamination with nuclear DNA. This technology allows us to study the effects of chemotherapeutic agents on mtDNA. Preliminary in vitro experiments have shown that cisplatin is capable of binding to mtDNA. Also I have demonstrated that cisplatin has a marked effect on cytochrome-oxidase activity – an enzyme whose catalytic subunits are coded by the mitochondrial DNA. Furthermore, electron microscopy has demonstrated morphological changes in number and shape of mitochondria in mice kidneys after cisplatin treatment.

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*CS-106.

**Career Scientist, OCTRF Hamilton Regional Cancer Centre; and Assistant Professor of Pathology, McMaster University, Hamilton.

In conclusion, these studies will provide a model system to designate molecular sites of DNA damage and also may elucidate the mechanism of toxicity, induced by various chemotherapeutic agents.

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ADDITIONAL INVESTIGATIONS

Dr. W.M. Hryniuk, Director of the Hamilton Regional Cancer Centre, reports on the following clinical research investigations:

ADJUVANT CHEMOTHERAPY FOR STAGE II BREAST CANCER

In co-operation with the London, Thunder Bay, and Windsor Regional Cancer Centres, we are conducting a randomized controlled trial to determine the efficacy of a short, intensive 12-week course of chemohormonal therapy compared with a standard 36-week course of chemotherapy. Benefit will be assessed with respect to reduction in recurrence rate and mortality; toxicity will be assessed in terms of side effects, associated morbidity, and reduced quality of life. On the one hand, if the shorter treatment yields failure rates that are similar, the expected decrease in toxicity would make the chemohormonal program a valuable addition to adjuvant therapy for Stage II breast cancer. On the other hand, if the shorter treatment is associated with a higher relapse and/or mortality rate this would help clinicians to decide on the optimal duration of adjuvant chemotherapy. To date, 220 women with Stage II disease have been randomized. This trial is supported by the Ontario Clinical Oncology Group and funded by the Medical Research Council of Canada.

QUALITY OF LIFE IN WOMEN RECEIVING ADJUVANT CHEMOTHERAPY FOR STAGE II BREAST CANCER

We have developed a new comprehensive index -- the Breast Cancer Chemotherapy Questionnaire, to measure toxicity and quality of life in women receiving adjuvant chemotherapy for breast cancer. Preliminary analysis suggests that this index is valid, reliable, and responsive to change. We have also used this clinical trial to explore the relationship between utility -- a measure of the worth of the health state, reported directly by the patient, and quality of life, as estimated indirectly by the quality of life questionnaires. We use a modified time trade-off technique, in which patients estimate how many years (in their present state of health) they would trade for a shorter life span in good health. The time trade-off method gives an estimate of the utility of quality of life while the patient is receiving chemotherapy. Utility may prove to be a useful measure of quality of life.

VENOUS THROMBOEMBOLIC DISEASE IN WOMEN RECEIVING ADJUVANT CHEMOTHERAPY FOR STAGE II BREAST CANCER

Although thrombosis has been described in a variety of solid tumors, these reports are anecdotal -- case series or case reports. No good case control or cohort studies have been done to determine the association (relative risk) between cancer and thrombosis. The postulated mechanisms for venous thrombosis in cancer patients are: (1) malignant cells induce clotting; (2) drugs used in the treatment of cancer produce thrombosis; and (3) associated conditions such as bed rest, surgery, and sepsis predispose to thrombosis. We are performing a cohort analytic study in which all patients receiving adjuvant chemotherapy for Stage II breast carcinoma undergo impedance plethysmography and Doppler ultrasound -- non-invasive examinations to detect deep-vein thrombosis, in order to determine the true rates of thrombosis in Stage II patients.

PILOT STUDIES IN STAGE IV BREAST CANCER

Phase II studies are being conducted in women with Stage IV breast cancer to: (1) measure the relationship between dose intensity and response of mitoxantrone; and (2) assess tolerance and response to a dose-intensive combination of fluorouracil, Adriamycin, and cyclophosphamide.

CO-OPERATIVE GROUP TRIALS

We are following selected protocols of the NCIC and OCOG for myeloma, Hodgkin's disease, non-Hodgkin's lymphoma, non-small-cell carcinoma of the lung, small-cell carcinoma of the lung, ovarian carcinoma, and Stage I breast cancer.

METHOTREXATE PHARMACOLOGY

We are participating in an NCIC sponsored study which will examine the influence of phenothiazine on metabolic conversion of methotrexate to 7-hydroxymethotrexate. Certain data suggest that phenothiazines may inhibit hepatic metabolism of methotrexate and that hepatic metabolisms of methotrexate may account for up to 30% of methotrexate clearance in patients receiving moderate to high-dose therapy. Since methotrexate clearance may influence clinical efficacy, it is important to learn about drug interactions which may influence clearance. Blood and urine levels of methotrexate and 7-hydroxymethotrexate are being examined in patients, randomly assigned to a phenothiazine anti-emetic or placebo.

CHEMOTHERAPY STUDIES IN HEAD AND NECK CANCER

A randomized controlled trial is being done to determine the optimum sequence for methotrexate and 5-fluorouracil in head and neck cancer. This trial will test a biochemical model which describes the interaction of the two drugs. The present sequence is a comparison of the standard therapy of simultaneous administration with another that provides an 18-hour delay between the two drugs. The trial is funded through NCIC, and to date 80 patients have been accrued.

In a separate study patients ineligible for the methotrexate/5-fluorouracil sequence are treated with standard-dose methotrexate and randomized to leucovorin rescue, or an identical placebo in a double-blind design. The aim is to determine the influence of leucovorin on the antitumor effect of standard-dose methotrexate and, at the same time, to determine the magnitude of protection from standard-dose methotrexate toxicity. Thus far, 22 patients have been accrued to the study, which is funded through Cyanamid Canada Inc.

STUDIES IN ACUTE MYELOBLASTIC LEUKEMIA

The Hamilton Centre is a founding member of the Leukemia Intergroup, funded through the National Institutes of Health, Bethesda, Maryland. This co-operative group of seven centres was established to seek laboratory and clinical predictors of treatment outcome in acute leukemia. All patients are treated on uniform protocols and laboratory studies are done on bone marrow and peripheral blood cells. Pharmacologic endpoints area also being measured. Current studies of high priority are: (1) an examination of the influence of chemotherapy on oncogene expression of freshly isolated leukemia cells; and (2) in vivo kinetics of leukemic cells using infusions of bromodeoxyuridine. Bromodeoxyuridine-labelled cells are identified in vitro using a monoclonal antibody to this compound.

STUDIES IN CANCER METASTASES

Dr. William Orr has an active program which examines factors that influence tumor-cell chemotaxis and the growth of metastases at different sites. The studies are funded by NCIC. His major interest is in variables that influence metastases of cancer cells to lung and bone; he will place special emphasis on the role of the inflammatory response in tumor-cell metastases and the role of bone resorption in bone metastases.

STUDIES ON ACTION MECHANISM OF ANTITUMOR DRUGS

Dr. Gurmit Singh is investigating mitochondria as a target for chemotherapeutic agents using, as a model, the influence of cis-platinum on nephrotoxity and on antitumor effects. He has developed a murine model for nephrotoxicity from cis-platinum and also has developed a method for identifying mitochondrial DNA as distinct from nuclear DNA within cells. With these methods, he hopes to distinguish between primary and secondary mitochondrial damage due to chemotherapeutic agents. The study is funded by the Medical Research Council of Canada.

STUDIES ON LIGHT DOSIMETRY, PHOTOSENSITIZER RADIOLABELLING FOR PHOTODYNAMIC THERAPY

As part of our NCIC-supported laboratory and clinical program on the development of photodynamic therapy (PDT) for treatment of solid tumors, Dr. Brian Wilson, in collaboration with Drs. P. Jeeves, M. Patterson and G. Firnau, is investigating:

- The optical properties of tissues and mathematical models of the propagation of light in tissues, with the application of reflectance spectrophotometry to quantitation of the concentration of photosensitizer in tissue.
- The labelling of the photosensitizer, hematoporphyrin derivative (HPD), with gamma- or positron-emitting radioisotopes for non-invasive quantitation of HPD concentration in tumor by external nuclear detection and/or emission tomography.
- A computer-controlled scanning spectroradiometer has been developed which enables in vivo measurements of the spatial distribution of light in tissue using

implanted optical fibre detectors. This instrument has been used to measure the changes in attenuation spectra in a range of animal tissues caused by changes in blood concentration and hemoglobin oxygenation. We are measuring the fundamental absorption and scattering coefficients of tissue, and using the results as input data to a Monte Carlo computer model of light transport. In collaboration with the University of Leeds, we are developing an optical method of HPD quantitation based on the reduction in the light diffusely reflected from tissue due to the absorption by HPD at 630 nm.

- HPD (and its main tumor-localizing, photoactive component, DHE) has been labelled with ^{64}Cu -- a positron emitter, which permits PET scanning to determine HPD concentration in tumor tissue. The effects of this labelling on HPD chemistry has been studied by extensive chromatographic analysis; also, the HPD biodistribution in tumor-bearing animals has been measured and compared with control values obtained with ^{14}C-HPD and by spectrofluorimetry. The results have confirmed the validity of studies using radiocopper-labelled HPD and DHE, and more detailed studies of intratumor distribution and tumor response are in progress using ^{64}Cu-DHE and ^{67}Cu-DHE.

Kingston Regional Cancer Centre

BASIC, DEVELOPMENTAL, AND CLINICAL CANCER RESEARCH*

J.C. KENNEDY**, *Kingston, Ontario*

Basic studies of the chemistry, photochemistry, and photobiology of hematoporphyrin derivative and Rhodamine-123 were carried out in collaboration with R.H. Pottier, J.-P. LaPlante, and A. Chow of the Royal Military College of Canada, Kingston, and T.G. Truscott of Paisley College, Scotland. With L. Beiner, we also studied the biosynthesis and photosensitizing properties of protoporphyrin IX in mice, rats, cats, bacteria, and mammalian malignant tissues.

Our ongoing engineering projects involve designing, constructing, and evaluating: (a) a simple and relatively inexpensive fluorescence bronchoscope for the detection of very early lung cancer -- in collaboration with P.C. Shragge and M. Bukowskyj; (b) improved light sources and light delivery systems for photochemotherapy in the vagina, urethra, and urinary bladder; (c) novel technology for inducing hyperthermia in superficial tumors; and (d) technology for the detection, identification, and quantitation of fluorescent materials in living animals -- in collaboration with R.H. Pottier, A. Chow, and J.-P. LaPlante.

We use our outpatient clinic for cats and dogs with various types of spontaneous cancer for the pre-clinical evaluation of experimental cancer therapies. In collaboration with veterinarian L. Beiner, we are studying the effectiveness of immunotherapy with staphylococcal protein A, and of photoradiation therapy with either hematoporphyrin derivative or protoporphyrin IX.

Our clinical trial of photochemotherapy for cancer began in 1978, and in the Kingston Regional Cancer Centre it is now considered to be more service work than research. Our clinical trial of hyperthermia involves only a few highly-selected patients, because our main research interest in this area lies in the development and clinical evaluation of our new technology. To the present, we have used staphylococcal protein A immunotherapy on an experimental basis in only two patients.

This project was supported by the Medical Research Council of Canada and/or the Department of National Defence and/or Pharmacia (Canada).

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*CS-101.

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STUDIES ON HUMAN CYTOTOXIC EFFECTOR CELLS*

H.F. PROSS**, *Kingston, Ontario*

The primary focus of our research in the past few years has been the study of human cytotoxic (antitumor) lymphocytes. These studies consisted of basic experiments into the fundamental mechanisms of killer-cell activity, and "clinical" experiments to determine the effect of malignant disease and its treatment. This report describes the more "clinical" experiments. Three types of cytotoxic lymphocytes have been studied: Natural killer (NK) cells; interleukin-2 activated killer (LAK) cells; and cytotoxic T cells. As the name implies, NK cells exist in the blood of all normal donors, from birth to old age. The level of NK activity is characteristic of the donor[1] and is decreased in patients with advanced malignant disease[2]. Recently we have concentrated on establishing valid methods of NK quantitation[3] so that we could make comparisons between patients and normals, or between patients at different stages of disease[4]. These methods are being applied to the analysis of several hundred patients with a variety of solid tumors to determine whether low NK activity has any prognostic significance in cancer patients. In other studies we did serial tests on a group of patients, who received lung cancer antigen in complete Freund's adjuvant (CFA) or CFA alone as part of the NCIC Bronchogenic 2 Trial, to determine the effect of such immunotherapy on NK activity[5]. It was found that the "immunization" caused a transient rise in NK activity, which peaked at 3-5 months and returned to normal after a year. NK activity also increased in 155 women tested repeatedly over a 5-year period while attending a breast-screening clinic because of "high risk" factors such as benign breast disease or family history[6]. When the "patients" were subdivided into subgroups, it was shown that NK activity was elevated in the group who had benign breast "disease", but was normal in those with positive family histories, but no breast disease. These observations help to increase our understanding of the interaction between host cytotoxic defenses and various benign conditions seen in cancer patients. A long-term study is underway to determine whether the ability to mount an enhanced cytotoxic response benefits the patient with cancer.

At the more basic level, we analyzed the NK and LAK activity of blood from a patient with mucolipidosis III – a genetic disorder caused by a defect in phosphotransferase activity[7]. This was done to test the hypothesis – based on sugar inhibition of NK lysis – that a mannose-6-phosphate receptor on tumor cells was essential for their lysis by NK cells. This hypothesis was disproved by the presence of very high NK and LAK activity in this patient and his family.

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*CS-102.

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In summary we have devised ways to quantitate NK-cell activity and have documented several instances where NK activity is suppressed or stimulated. The prognostic significance of these findings is under study.

This project was funded by MRC and NCIC.

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HUMAN MONOCLONAL ANTIBODIES: APPLICATION TO CANCER*

S.P.C. COLE** and B.G. CAMPLING†, *Kingston, Ontario*

Since Kohler and Milstein described the production of murine monoclonal antibodies of predetermined specificity in 1975, many have attempted to produce human monoclonal antibodies by similar techniques. Mouse monoclonal antibodies have had a major impact on the diagnosis of human malignancies and even have been used in the treatment of some cancers. However, many patients so treated, have developed antibodies to the mouse immunoglobulins thus limiting further treatment. Human monoclonal antibodies should be far less immunogenic, although there might still be an anti-idiotypic response. Despite the predicted advantages of human monoclonal antibodies, the technology for their production has lagged behind that of mouse monoclonal antibodies. The following projects are underway in our laboratory to improve current human monoclonal antibody technology: (1) production of an optimal, human myeloma fusion partner with the necessary drug resistance markers for hybrid selection; (2) enrichment of antigen-specific, human B lymphocytes by in vitro immunization, and pre-selection techniques; and (3) mass production of human monoclonal antibodies using serum-free, large-scale tissue culture techniques.

This project was funded by NCIC.

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*CS-107.

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BIOLOGICAL BASIS OF DRUG RESISTANCE IN HUMAN TUMOR CELLS*

S.P.C. COLE**, *Kingston, Ontario*

The development of resistance to antineoplastic agents is a major problem in clinical oncology. Studies in rodent model systems suggest that alterations in cell surface glycoproteins (P-glycoproteins) are a general phenomenon associated with, and responsible for, the multi-drug resistance phenotype. Few human tumor models are available for study. Recently in my laboratory, we have isolated a multi-drug-resistant, human small cell lung cancer cell line. This cell line and other drug-resistant human cell lines being developed will be used to immunize mice with a view to generating a panel of murine monoclonal antibodies specific for drug-resistant human cells. Monoclonal antibodies, which can recognize individual and related forms of the human equivalent of P-glycoprotein, would be extemely useful in the assessment of heterogeneity of expression of drug resistance, within and among human tumor cell lines and human cancer tissue samples. By themselves or conjugated to a toxin, these antibodies may help us overcome drug resistance in tumor cells in cancer patients.

This project was funded by MRC.

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*CS-107-1.

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London Regional Cancer Centre

USE OF NUCLEAR MAGNETIC RESONANCE TO MONITOR TISSUE DAMAGE CAUSED BY IONIZING RADIATION OR CYTOTOXIC CHEMICALS*

W.R. INCH**, *London, Ontario*

Two projects are being investigated: the first, a method to monitor lung damage produced by x-rays or bleomycin using data obtained from a whole body imager (MRI); the second is an investigation of cardiac damage caused by Adriamycin using 31P spectra obtained from a small bore (30 cm diameter) super-conducting system (MRS).

Assessment of Lung Damage Using MRI

This project was designed to determine whether nuclear magnetic resonance (NMR) could be used to monitor lung injury produced by ionizing radiation or cytotoxic chemicals. A high and low dose of x-rays are used and the chemical, bleomycin, is instilled by the intratracheal route. The first experiments looked at the high dose of x-rays, 14 Gy, which produces pneumonitis. To date we have treated the right lung of 45 Wister rats; 41 are being evaluated on a continuing basis. The animals were imaged in the head coil of the Technicare whole-body imager, and proton relaxation times (T1 and T2) were calculated for each lung, at various times up to 200 days after treatment. Pneumonitis was confirmed at 20 days by a pathologist, who examined fixed sections of the lung in a double-blind test.

Normalized T1 values decreased for three weeks after treatment. By day 60 they increased and were nearly 30% longer than T1 for control lungs. By 100 days they decreased again and resembled the control values. The T2 values increased by 30% up to 8 days and were 20% less than the controls at 100 days. After the injection Tc-99m macroaggregate, the gamma-scan of the lungs did not have the high resolution obtained by MRI. However, gamma-counts from the lungs indicated an initial 20% increase in blood flow, followed by a marked 70% decrease by day 60.

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*CS-100.

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which persisted to day 100. We conclude that MRI can be used to monitor lung injury following treatment by x-rays.

Assessment of Cardiac Damage Caused by Adriamycin

Adriamycin, a widely used cytotoxic agent that is effective against many human tumors, has a number of reversible side effects, such as leukothrombocytopenia, anemia, nausea, vomiting and alopecia. Its effect on the heart muscle often is not reversible.

We are studying the development of Adriamycin-induced cardiotoxicity in the cat. Nuclear magnetic resonance spectroscopy (MRS) is used to measure the heart's 31P spectra. Cardiac ejection fraction is determined using Tc-99mm and an elctrocardiogram is recorded at regular intervals over a period of four months. Histologic sections of endocardium and epicardium will be made at two, three and four months.

MRS, a non-invasive technique, may be able to predict the onset of cardiotoxicity as well or better than current methods. Such a prediction would allow the therapist to change to a less toxic drug or give a free-radical scavenger, such as Vitamin E or butylated hydroxyanisole, in an attempt to prevent or reverse myocardial damage. Since blood flow to the myocardium is considerably larger than to most tumors, an antioxidant administered before Adriamycin should reach a higher concentration in the heart, and thus yield a therapeutic advantage. Important factors in choosing a chemical protector would be the rate of increase and clearance times of the two drugs in the heart and tumor.

When this proposal was drafted, we had operated upon two animals. Removal of ribs and skeletal muscle took about three hours. A "Marlex" window was inserted in the chest and the chest closed using standard surgical technique. The single-turn, copper coil is placed directly beneath this "window" and the animal's chest is aligned so that the coil obtains its signal only through the chest "window". Proton and phosphorus spectra have been obtained from both animals one week after operation. It takes about 30 minutes to collect sufficient signal.

The use of 31P MRS also may be useful in assessing other types of cardiac damage, such as coronary artery disease, cardiomyopathy due to chronic diabetes, or changes in myocardial metabolism due to atherosclerosis.

SYNTHESIS AND REGULATION OF AMPLIFIED METALLOTHIONEIN-I GENES IN VIVO*

J. KOROPATNICK**, *London, Ontario*

Gene amplification -- a process which allows us to induce a greater-than-normal complement of a specific genes or DNA sequence in cells -- recently has been proposed as a mechanism for controlling gene expression in eukaryotic somatic cells, and as a marker for transformation and metastatic potential in tumor cells[1].

We have encountered specific, in vivo, amplification of the gene for mouse metallothionein-I (MT-I) after exposure to an inducer of expression of that gene (cadmium)[2]. This is the only reported example of induced gene amplification in a whole animal. In addition, we have demonstrated variation in MT-I gene copy number during embryonic mouse development in liver, but not brain. We propose to exploit this inducible and developmental variation in MT-I gene copy number as a model to determine: (a) the nature of in vivo MT-I gene amplification; and (b) the nature of action of modifiers of gene amplification, DNA-damaging agents and cell-cycle inhibitors on MT-I gene copy number, chromatin structure and transcription.

As we have shown, MT-I genes exhibit variation in copy number during development; indeed, there is an approximate five-fold increase in MT-I gene copy concentration in bulk DNA in late embryo mouse liver in comparison with adult mouse liver DNA. In addition, there is a two- to three-fold increase in MT-I gene copy concentration within six hours of treatment of adult mice with high levels of cadmium sulphate. We suggest that copy number increase and decrease may take place through preferential replication of a subset of mouse liver cells that have a constitutive high MT-I gene copy number relative to surrounding liver cells; this is more likely than by the sequential replication and degradation of MT-I genes with respect to the bulk of DNA. The observation that mouse sperm DNA has an elevated MT-I gene copy concentration in comparison with adult mouse liver, brain and kidney DNA, suggest that germ-line and early diploid cells may contain multiple MT-I gene copies which are lost in some subset of cells during embryogenesis. We are engaged in the culture and propagation of subpopulations of mouse liver cells to determine whether such subset exists, and to create a cultured cell gene amplification model that would parallel that observed in mouse.

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*CS-103.

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GENETICS OF TUMOR PROGRESSION AND METASTASIS*

A.F. CHAMBERS**, *London, Ontario*

An experimental metastasis assay in the immune-deficient embryonic chick[1] is being used to analyze the molecular genetics of tumor metastasis. Two approaches are employed. First, genomic DNA from metastatic cells is "transfected" into non-metastatic recipient cells. This approach has resulted in the successful transfer of experimental metastatic ability[2]. The nature of the gene or genes responsible is being examined. Second, the role of specific oncogenes in aspects of the metastatic phenotype is being examined. We have found that a temperature-sensitive viral src oncogene can confer metastatic properties at the permissive temperature but not at the non-permissive temperature[3]. Also we have found that the human bladder-cancer oncogene (T24-H-ras) can confer metastatic properties on NIH3T3 cells.[4]

A synthesis of this work and work of others leads us to propose a model for the kinds of changes necessary in tumor progression to a fully metastatic phenotype. First, cells must acquire intrinsic metastatic ability, as detectable in assays in immune-deficient hosts. Second, cells must acquire the ability to escape immune destruction in immune-competent hosts. The relationship between these distinct phenotypes is being examined.

In a related project, working with Dr. J.F. Harris, we are studying the somatic cell genetic properties of metastatic cells, using assays in immune-competent hosts. We have observed that some metastatic properties are unstable in their expression, and are examining the nature of this instability.

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*CS-150.

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APPLICATIONS OF MONOCLONAL ANTIBODIES TO METASTASIS*

J.F. HARRIS**, *London, Ontario*

Mouse and human embryonal carcinoma (EC) cells are being studied as a source of oncodevelopmental antigens and as a model of metastasis, which may involve differentiation.

Monoclonal antibodies (MAb) have been developed to two distinct families of oncodevelopmental antigens of mouse and human EC cells. The binding and functional properties of the anti-SSEA-1 MAb 3A1 and AB1 (IgM isotope) have been reported previously[1]. A family of mutually competitive IgG isotype MAb (eg. 90-1, 22) identify a distinct differentiation antigen of mouse and human EC cells. The treatment of mouse and human EC cells with retinoic acid initiates a time-dependent expression of SSEA-1 antigen and a transient appearance of the new antigen. Fluctuation of both 90-1 and SSEA-1 may occur during routine culture; however, the changes in the new antigen expression are much larger.

Natural killer (NK) cells may be important effector cells in the host defence against metastatic cells. In an attempt to examine for possible involvement of antibody in the NK cytotoxicity, MAb against oncodevelopmental antigens was added to NK assays in vitro. Both MAb of anti-SSEA-1 family[1] and MAb of the new antigen family are inhibitory. This finding is being applied to better define the receptor systems of NK cells.

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*CS-151.

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QUANTITATIVE STABILITY ANALYSIS OF HUMAN MONOCLONAL ANTIBODY PRODUCTION BY HETEROMYELOMA HYBRIDOMAS USING AN IMMUNOFLUORESCENT TECHNIQUE*

J.S. GARDNER** and J.F. HARRIS†, *London, Ontario*

We have described the quantitative analysis of the stability of human monoclonal antibody production by hybridomas. Clones derived from fusion between the SHM-D33 heteromyeloma line and EBV-stimulated human lymphocytes were studied for antibody presence using a fluorescent-labelling technique. By measuring the frequencies of antibody-negative variants in clonal populations grown to a measured cell number, the rates of generation of antibody-negative cells were calculated using Luria-Delbruck fluctuation analysis and methods of analysis that are employed to detect the appearance of metastatic variant cells[1,2]. Stability was variable for independent hybridoma lines, and the corresponding rates were in the range of 15×10^{-4} to 6×10^{-2} /cell/generation. The stability of the more stable heteromyeloma hybridomas approached that observed in mouse-mouse hybridomas. There was a positive correlation between frequency of antibody-negative variants measured in clonal populations grown to large numbers of cells ($>10^7$ per culture) and their rate of loss of antibody production. High frequencies of antibody-negative variants may predict the imminent loss of antibody-producing capacity by a clone growing in suspension culture.

These results suggest that human monoclonal antibody production by heteromyeloma hybridomas yield lines with acceptable stability.

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*CS-170.

**NCIC Terry Fox Fellow.

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SURFACE ANTIGENS OF CULTURED HUMAN ASTROCYTOMAS: MARKERS FOR ASTROCYTOMA SUBSETS AND ASTROCYTE DIFFERENTIATION*

J.G. CAIRNCROSS**, *London, Ontario*

We continue to study the patterns of expression of astrocyte differentiation antigens on cultured human astrocytomas. Previous work has suggested that, when considered with morphology in culture and glialfilament expression, cell-surface markers provide a basis for subgrouping cultured astrocytomas. An immunopathological classification of astrocytomas and other glial tumors may augment conventional light-microscopic assessment and influence prognosis and selection for treatment. We are also studying the effects of culture conditions and differentiation-inducing agents on glial filament expression in human astrocytomas.

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*Project 471. (Final Report)

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University of Western Ontario, London

THE EFFECT OF SOCIOECONOMIC STATUS ON THE PROGNOSIS OF CANCER OF VARIOUS SITES*

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and J.E. KINCADE‡, Chapel Hill, NC, USA

The purpose of this study is to determine whether socioeconomic status (SES) has an effect on the prognosis of cancer of several sites, especially breast, lung, large bowel, endometrium, cervix and the lymphatic system (lymphomas). In particular, we are testing the hypothesis that cancer has a poorer prognosis (low survival rates) among persons of low SES than among persons of high SES, even when other important factors such as stage of disease and method of treatment are the same.

After taking into account the effect of stage, pathologic type of tumor, and treatment, we found no convincing evidence that cancer patients of low SES, measured by either education or occupation, had a poorer outcome at one year after diagnosis from cancers of all sites combined or lung cancer specifically. We plan to follow the patients in this study at least to five years after the interview to see whether any SES effects are seen at that time, especially among those patients who, by virtue of early disease at diagnosis, had a favorable one-year prognosis. Meanwhile, the results indicate either that SES has no effect on short-term cancer prognosis or that such effects are removed in the Ontario Cancer Treatment and Research Foundation's system where SES operating through ability to pay does not influence admission and treatment.

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*Project 420. (Final Report)

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Ottawa Regional Cancer Centre

INVESTIGATION OF THE POSSIBLE ROLE OF OXYGEN RADICALS IN TUMOR PROGRESSION AND TUMOR-CELL HETEROGENEITY*

H.C. BIRNBOIM**, *Ottawa, Ontario*

The term "tumor progression" refers to the progressive changes seen in many tumors during the course of malignant disease. Not only do tumors increase in size with time, but they may become invasive and metastatic. At a cellular level, changes are seen frequently in the chromosomes, and in a variety of histochemical and biochemical parameters. Is this apparent genetic instability of tumor cells an innate property of the tumor cell or something in the tumor environment responsible for these progressive changes? We have begun to investigate the possibility that macrophages and neutrophils and other phagocytic cells within solid tumors may contribute to this apparent variability.

As a model system we use a mouse fibrosarcoma that is maintained by serial passage subcutaneously in mice; also it can be maintained in cell culture. The tumor has been stable on serial passage. Our approach was to inject an agent, which might stimulate phagocytic cells to generate oxygen radicals, to determine if we could induce and demonstrate changes within the tumor-cell population. When phorbol ester was injected, it induced a dramatic change; the tumor ulcerated and became necrotic within a day or two after injection. We now believe that this agent promotes the production of a "tumor necrosis factor" which caused the observed necrosis. At the same time, we sought to demonstrate whether there was also an inheritable phenotypic change. To test for this, we injected cells from the necrotic tumor into animals that had been immunized against the original parental tumor line. Under these conditions, the animal develops a cellular immunity against the transplanted tumor and the parental line will not grow. However, cells from necrotic tumors, when injected into immunized animals, did produce tumors. These experiments suggest that we are inducing necrotic factor and tumor phenotypic variability, although other explanations are possible. We are investigating the mechanism of this apparent induction of tumor-cell heterogeneity.

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*CS-104.

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MECHANISM OF OXYGEN-RADICAL DAMAGE TO CELLULAR DNA AND ITS ROLE IN TUMOR PROMOTION*

H.C. BIRNBOIM**, *Ottawa Ontario*

In recent years, many workers have shown increasing interest in the possibility that oxygen radicals may be important in a variety of human conditions, including aging, tumor initiation and promotion, and tissue injury following ischemia. We have been interested particularly in the possibility that one oxygen radical (the superoxide anion) may play a role in carcinogenesis and tumor promotion. Because oxygen radicals, such as superoxide anion and hydrogen peroxide, occur naturally in virtually all cells exposed to oxygen, we have concentrated our attention on the effects that low levels of these radicals may have on cells. These oxygen radicals arise in cells within mitochondria and other subcellular organelles. Their major source within the body is the respiratory "burst" of phagocytic cells such as neutrophils, i.e., the burst of oxygen radicals produced by these cells on contact with bacteria and other stimulants.

Our experiments are carried out with human peripheral blood leukocytes obtained from volunteers within the cancer centre and the adjacent medical school. On a daily basis, we obtain approximately 50 ml of blood from which we isolate a fraction enriched in neutrophils. These cells are exposed to a phorbol ester tumor promoter (TPA) and incubated for periods up to 40 min at 37°C. During this time, the cells suffer no microscopically visible changes, but analysis by a fluorometric technique (developed earlier in our laboratory) shows that strand breaks occur in the genomic DNA. These breaks involve oxygen radicals produced by the neutrophils on exposure to TPA. Simultaneously the cells are monitored for their ability to produce oxygen radicals and for the appearance of strand breaks in their DNA. Other cellular components, such as ATP, are also measured. Our current experiments lead us to conclude that the oxygen radical, superoxide anion, introduces breaks in DNA by a mechanism which is different than that induced by ionizing radiation. We believe that damage by radiation is principally due to the hydroxyl radical acting directly on DNA. By contrast, superoxide anion generated outside the cell appears to cause damage to DNA by a mechanism which involves metabolic processes. Since superoxide anion is not a highly reactive radical species, we believe that it acts through a specific metabolic pathway culminating in a change in the DNA. We are investigating this pathway further.

This project was supported by a grant from the MRC.

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*CS-104-1.

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ROLE OF DNA(CYTOSINE)-METHYLATION IN TUMOR PROGRESSION AND TUMOR-CELL BIOLOGY*

R.G. LITEPLO**, *Ottawa, Ontario*

An important objective in tumor-cell biology is to identify the mechanisms and processes underlying the generation of tumor-cell heterogeneity and tumor progression. While much emphasis has been placed on genetic (mutational) mechanisms, it is clear that epigenetic processes, i.e. alterations in gene expression, also are important. It has been proposed that one epigenetic process, namely, DNA(cytosine)-methylation may play an important role in the diversification and progression of tumor-cell populations. However, before we can understand the manner and extent to which changes in DNA(cytosine)-methylation contribute to these processes, we require a better understanding of the process itself and the factors involved in its regulation.

As a first step towards obtaining a better understanding of how changes in the level of 5-methylcytosine in DNA may contribute to these aspects of neoplasia, we will study the stability of drug-induced alterations in DNA(cytosine)-methylation in a variety of murine and human cell lines of defined tumorigenic and metastatic potential. The total 5-methylcytosine level and the methylation of certain oncogenes will be measured at various times after drug treatment. In addition, the methylation level and transcriptional activities of specific oncogenes are also being examined in a series of related human or murine tumor-cell lines of defined metastatic potential.

We have found that the reduction in the methylation of DNA (following the in vitro treatment of a variety of murine tumor-cell lines with 5-azacytidine) is rapidly reversed following removal of the drug. This suggests that the genomic wide reduction in 5-methylcytosine levels are not necessarily maintained, even in those cases where the drug has a significant effect on the phenotypic properties of those cells.

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*CS-108.

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ADDITIONAL INVESTIGATIONS

Dr. G.E. Catton, Director of the Ottawa Regional Cancer Centre, reports on the following clinical research investigations:

In 1984, 339 patients were entered on clinical trials, and patient accrual in 1985 continued at an average rate of 30 patients per month. Currently, there are 47 active clinical research protocols.

TREATMENT OF BREAST CANCER

Investigators continue entering patients into the National Surgical Adjuvant Breast Project (NSABP) protocols to determine the effect of adjuvant chemotherapy and hormonal therapy in breast cancer patients according to the age of the patient, stage, and estrogen and progesterone receptors. Postmenopausal Stage II patients are entered on the NCIC MA.4 or NSABP studies.

Surgeons and radiation oncologists are contributing patients to the Ontario Clinical Oncology Group Stage I breast carcinoma study, assessing the effectiveness of breast radiation following partial mastectomy and axillary dissection.

Patients with advanced breast cancer are eligible for participation in a study of Megace vs tamoxifen, if they are ER positive. Those failing tamoxifen and ER-negative, they become candidates for the NCIC Phase II trial of flutamide. Patients failing on or not eligible for these regimens are candidates for a study comparing cyclophosphamide, Adriamycin and 5-FU to cyclophosphamide, Novantrone and 5-FU. A Phase I study assessing the combination of Adriamycin and mitoxantrone in Stage IV breast carcinoma was completed recently and results of this are pending. The NCIC Phase II study of menogaril in patients with no prior chemotherapy for advanced disease will be activated shortly, and also an NCIC Phase II trial of tiazofurin for disease refractory to front-line chemotherapy.

CURRENT STUDIES IN LYMPHOMA

The lymphoma group continues to contribute patients to the NCIC-sponsored trials, including the escalated BACOP/Septra study in poor-prognosis, non-Hodgkin's lymphoma, and the MOPP/ABV hybrid versus alternating MOPP/ABVD for advanced or recurrent Hodgkin's disease. The NCIC Phase II study of Acivicin as second-line therapy in poor-prognosis lymphomas is now active. A Phase II study of tamoxifen is planned.

GASTROINTENSTINAL PROTOCOLS

The NSABP colon study, evaluating the postoperative portal-vein infusion of 5-FU and sodium heparin in patients with resectable adenocarcinoma, is open for patient entry.

Radiation oncologists will participate in a study assessing the effectiveness of whole abdominal radiation in resectable colon cancer.

Patients with metastatic colon cancer were entered into a recently completed, Cyanamid-sponsored, NCIC study of sequential 24-hour infusions of methotrexate and 5-FU with leucovorin rescue. Currently, patients with advanced colon and pancreatic cancers are eligible for entry of Phase II trials of tiazofurin.

GYNECOLOGICAL/GENITO-URINARY TRIALS

Patients with ovarian carcinoma are being entered into NCIC-sponsered trials. A study of intraperitoneal cisplatin is planned.

Patients with prostate cancer are eligible for studies of orchiectomy plus flutamide. Those refusing orchiectomy are eligible for studies of Megace plus stilbestrol versus stilbestrol alone.

Patients with superficial bladder cancers, which recurred after front-line intravesical therapy, are candidates for a Phase I and pharmacologic study of intravesical mitoxantrone. Patients with locally advanced bladder cancer are eligible for a study of intra-arterial cisplatin plus radiotherapy plus/minus cystectomy. Patients not eligible for this treatment remain candidates for a study of intra-arterial cisplatin plus disulfiram. Patients with metastatic bladder cancer are eligible for a study of I.V. cisplatin plus disulfiram, and a Phase II study of menogaril is planned.

Patients with advanced renal-cell carcinoma are being entered on a study of mitomycin-C plus metronidazole, and a Phase II study of menogaril is planned, based on activity noted in a Phase I study.

EAR-NOSE-THROAT STUDIES

Patients with advanced carcinoma of the larynx and hypopharynx are candidates for the PMH protocol, which attempts to determine whether concurrent irradiation, 5-FU infusion and mitomycin-C improves the local and regional control, and survival over radiation therapy alone. Patients with primaries in other sites are candidates for a study of lonidamine plus radiotherapy. Patients with disease recurrent after radiation are eligible for a Phase II trial of high-dose mitoxantrone. A study of doxorubicin plus metronidazole has been completed.

Patients receiving radiotherapy for ear-nose-throat malignancies are candidates for a study to determine whether indomethacin reduces radiation mucositis.

BRAIN TUMOR TRIALS

Patients with intracerebral tumors recurrent after cranial irradiation are candidates for a Phase I NCIC study of intracarotid PCNU. Patients with brain metastases recurrent after irradiation also are eligible for a Phase II trial of intracarotid mitomycin-C. A Phase I-II study of a multidrug combination of intracarotid plus systemic chemotherapy recently was completed, as was Phase II studies of I.V. mitoxantrone and Phase I-II studies of cisplatin plus cytosine arabinoside plus caffeine. A study of an intrathecal combination of methotrexate, hydrocortisone, cytosine arabinoside, and thio-TEPA for meningeal carcinomatosis also has been completed. Studies planned for the near future include interstitial irradiation combined with external beam irradiation and intracarotid BCNU plus VM-26 plus cisplatin as front-line treatment of "good-prognosis" glioblastoma patients, radiotherapy plus lonidamine for brain metastases, and intracarotid interferon for patients with recurrent disease. Over the past three years, approximately 100 patients have been treated on various investigational intracarotid chemotherapy protocols.

LUNG CANCER

Radiation oncologists are assessing the effectiveness of adjuvant fractionated half-body radiotherapy in non-small cell lung cancer. Patients with inoperable, limited non-small cell lung cancer are eligible for a study of lonidamine plus radiotherapy. Patients with recurrent or metastatic disease are candidates for the NCIC Phase II trial of tiazofurin or a Phase I trial of cisplatin plus acivicin. A Phase II trial of trimetrexate is planned.

Patients with limited small-cell lung cancer are candidates for the NCIC study of early vs late radiotherapy combined with chemotherapy. Patients with recurrent or metastatic disease are eligible for a Phase II trial of tiazofurin.

MELANOMA STUDY

Patients with Stage I disease are eligible for the intergroup study of wide vs limited excision. Patients with metastatic disease are candidates for a study of interferon plus DTIC. Participation in the NCIC Phase II menogaril study is planned.

SARCOMA

Patients with metastatic disease are candidates for the NCIC Phase II trial of mitoxantrone.

MISCELLANEOUS STUDIES

In progress are active Phase I studies of weekly I.V. menogaril and of cisplatin plus disulfiram. A Phase I and pharmacology study of tiazofurin and a comparison of the toxicity and bioavailability of three different oral cyclophosphamide preparations have been completed. Phase I studies are planned of didemnin, oral menogaril, and oral idarubicin.

CLINICAL PHARMACOLOGY STUDIES OF ANTINEOPLASTIC AGENTS

Dr. D.J. Stewart and his colleagues have carried out a number of clinical pharmacology studies in collaboration with other Ottawa investigators. Studies of cisplatin pharmacology were done in collaboration with Drs. N. Mikhael, A. Ninji, R.C. Nair, S. Kacew, J. Maroun and W. Hirte. These studies showed that cisplatin nephrotoxicity is proportional to renal cortex and medulla, the cumulative cisplatin dose, and the pretreatment serum uric acid. Nephrotoxicity is inversely proportional to serum albumin. Based on these findings, we plan to initiate studies of cisplatin plus allopurinol and cisplatin plus albumin infusions. A unique cisplatin-induced glomerular lesion (glomerulomegaly) was noted. Autopsy liver platinum concentrations were poroportional to cumulative cisplatin dose. The decrease in serum albumin over the course of cisplatin treatment also was proportional to platinum concentrations in liver post mortem, suggesting the possibility of cisplatin induced hepatic toxicity. Tumors in liver were found to have higher platinum concentrations than tumors in other parts of the body. We constructed a multiple linear regression equation to predict platinum concentrations in individual tumors. Work continues to further define factors that affect platinum concentrations in various tissues, and to determine the relationship between tissue-platinum concentrations and cisplatin toxicity and efficacy. In collaboration with the above investigators and H. Hugenholtz, studies are being initiated to determine the effect of various factors on uptake of cisplatin into the rat intracerebral 9L gliosarcoma model.

Studies of mitoxantrone are underway in collaboration with R.M. Green, H. Hugenholtz, M. Richard, L. Goumnerova, N. Mikhael and V. Montpetit. High mitoxantrone concentrations were found in brain tumors resected from 10 patients who had consented to the administration of low dose mitoxantrone intravenously before operation. Consistently tumor mitoxantrone concentration was higher than concurrent plasma mitoxantrone concentration. Studies on autopsy tissues from 10 patients who received mitoxantrone before death revealed that the drug persists in tissues for several months after administration. High concentrations also have been noted in the heart.

Studies of tiazofurin in collaboration with R.M. Green, J.A. Maroun, H. Hugenholtz and M. Richard revealed that this agent penetrates rapidly into human intracerebral tumors, but the drug concentration in tumors is generally lower than concurrent plasma concentrations. Plasma pharmacokinetics conform to a two-compartment model and the elimination half-life is approximately 6 hr. Uptake into erythrocytes is rapid, and disappearance from erythrocytes closely parallels that seen in plasma. Renal excretion accounts for much of the elimination of the drug. Toxicity is proportional to the area under the plasma tiazofurin concentration-times-time curve, and is inversely proportional to plasma clearance of the drug.

Studies of uptake of teniposide into human brain tumors were done in collaboration with H. Hugenholtz and M. Richard. Higher drug concentrations were achieved in brain metastases than in gliomas. Pretreatment with oral glycerol appeared to augment drug penetration into brain tumors, while pretreatment with amphotericin-B and prolonging the duration of drug infusion did not increase tumor teniposide concentrations. Studies are being done in a rat intracerebral 9L gliosarcoma model in collaboration with H. Hugenholtz and R.M. Green to examine the effect of glycerol on uptake of VM-26 into brain tumors.

Recently we have completed a study of gastrointenstinal toxicity and bioavailability of three different oral cyclophosphamide preparations. The data are being analyzed.

Plasma sample have been collected for pharmacokinetic studies from patients who have participated in a Phase I study of menogaril given once weekly intravenously and currently are undergoing analysis.

Thunder Bay Regional Cancer Centre

CLINICAL INVESTIGATIONS

Dr. J.F. Kotalik, Director of the Thunder Bay Regional Cancer Centre, reports on the following clinical research investigations:

ADJUVANT CHEMOTHERAPY FOR BREAST CANCER

Patients are being entered into the Ontario Clinical Oncology Group (OCOG) Stage I trial to determine the effectiveness of breast irradiation following partial mastectomy and axillary dissection in node-negative patients with carcinoma of the breast. Patients with node-positive disease are being entred into OCOG Stage II trial, which compares intensive short-course chemohormonal therapy with a standard extended course of chemotherapy. Those patients who are postmenopausal and node-positive are being entered into the NCIC study which is assessing tamoxifen with or without chemotherapy.

METASTATIC BREAST CANCER

We are participating with the North Central Cancer Treatment Group (NCCTG), led by the Mayo Clinic, in trials involving various combinations of cyclophosphamide, methotrexate and 5-FU in patients with metastic breast cancer. Patients who have failed on such regimens are being entered into studies which are comparing the use of Adriamycin as a single agent, with the same drug in combination with vincristine and mitomycin-C.

TRIALS IN LUNG CANCER

The Thunder Bay Centre is participating in NCCTG trials involving the use of various mitomycin-C regimens for patients with metastatic non-small cell carcinoma of the lung. Patients with locally unresectable diseases are being offered the opportunity to participate in studies comparing the use of radiotherapy alone with combined radiation and chemotherapy. Before activation of the above studies, patients were being entered onto the NCIC trial for patients with metastatic disease comparing supportive care with standard chemotherapy combinations.

This Centre also participates in the NCIC trial which compares early and late radiation therapy in association with chemotherapy for limited small cell carcinoma of the lung.

STUDIES IN GYNECOLOGICAL MALIGNANCIES

The Centre has actively participated in the NCIC ovarian trials and anticipates expanding its role by activating a comparison of a trial of cyclophosphamide/cis-platinum versus cyclophosphamide/carboplatinum as first-line treatment for advanced ovarian carcinoma.

STUDIES IN MULTIPLE MYELOMA

Patients are being entered into the NCIC trial investigating the possible effectiveness of etidornate disodium as an adjuvant therapy in the treatment of multiple myeloma. Also we have activated the NCIC trial of 2-deoxycoformycin in the treatment of leukemic reticuloendotheliosis and patients are being entered into this study.

GASTROINTESTINAL MALIGNANCY

We are actively participating in the NCCTG study, which is testing various combinations of 5-FU, methotrexate, calcium leucovorin and cis-platinum in the treatment of metastatic colorectal carcinoma.

MALIGNANCY OF THE CENTRAL NERVOUS SYSTEM

Under the auspices of an NCCTG trial, we are exploring the value of combined modality therapy with the nitrosoureas BCNU and PCNU in the treatment of glioblastomas.

It is anticipated that studies involving epirubicin for the treatment of extensive small-cell carcinoma of the lung, carcinoma of the prostate, and/or metastatic carcinoma of the breast will be activated within the next year. Activation of selected studies is being considered under the auspices of the National Surgical Adjuvant Breast and Bowel Project (NSABP) and it is expected that this study will be open to accrual within the next year.

Hospital for Sick Children, Toronto

ASSESSMENT OF VARIOUS CHEMOTHERAPEUTIC REGIMENS IN PEDIATRIC MALIGNANCIES IN CO-OPERATION WITH THE CHILDREN'S CANCER STUDY GROUP*

M.J. SONLEY** and R.D.T. JENKIN†, *Toronto, Ontario*

For the past 16 years the grant has enabled the members of the Department of Pediatrics at the Princess Margaret Hospital, and the Department of Hematology-Oncology at the Hospital for Sick Children to participate in the therapeutic trials of the Children's Cancer Study Group (CCSG), and to participate in several local studies and an NCI study[1,4].

After the first two years, when a research fellow was supported, the grant provided funds for statistical assistance and for travel to the triannual CCSG meetings.

Twenty-five pediatric institutions in North America took part in the design and conduct of the CCSG trials. In the last 16 years the prognosis in childhood malignancy has improved dramatically, and much of this is due to the clinical trials of the CCSG.

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. Without treatment it is always fatal within a few months, but, as the result of a succession of controlled chemotherapy trials, at least 70% of children with ALL are alive and well and off all treatment five years from the time of diagnosis. It is expected that the disease will not recur in most of these children. Also, prognostic factors have been identified which allow us to select, at the time of diagnosis, which children require minimal, moderate, or very extensive treatment in order to eradicate the disease.

In children with Wilms' tumor[2] the percentage of children alive and well five years after diagnosis increased from 40% to 80% when chemotherapy was added to radiotherapy and surgery. Recurrence after five years from diagnosis is extremely rare in Wilms' tumor and in most tumors of childhood. Several groups of children have been identified who require more or less vigorous treatment than the "standard".

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*Project 204. (Final Report)

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Hodgkin's disease[3] in all stages now can be cured in the majority of children. At least 90% of children are alive and well five years after diagnosis. Non-Hodgkin's lymphoma also has responded dramatically to recent changes in chemotherapy.

In the past, less than 10% of children with osteogenic sarcoma survived, but now with a combination of surgery and chemotherapy over 70% are alive and well five years later.

In children with astrocytoma of the brain, chemotherapy given in addition to radiotherapy has been shown to increase the survival rate. New chemotherapy trials are underway.

On the other hand, there has been no improvement in the survival of children with neuroblastoma[5] -- a common tumor of the sympathetic nervous system, although we have tried a variety of combinations of radiotherapy, chemotherapy and immunotherapy. Currently we are studying the effects of bone-marrow transplantation.

CCSG and local trials have demonstrated the effectiveness of several new chemotherapeutic agents in children[6]. Also, because of the large number of children enrolled in each CCSG study, much has been learned about the epidemiology, etiology, clinical characteristics and prognostic factors of pediatric malignancies. This knowledge will help in the development of future therapeutic protocols.

As a result of two decades of therapeutic trials, the treatment of pediatric cancer now is so successful that the therapeutic emphasis has changed. Rather than continuing to add more treatment in order to increase the rate of cure, several of the current CCSG protocols are studying the effect of giving fewer drugs in smaller doses for a shorter period of time, in order to reduce the acute and long-term complications of the treatment. We now are able to direct our effort at curing the child with the least possible treatment so that he or she will become a productive and physically, emotionally and sexually normal adult.

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HETEROGENEITY OF ACUTE LYMPHOCYTIC LEUKEMIA OF CHILDHOOD*

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For the last several years, we have focussed on the analysis of the heterogeneity of childhood leukemia in order to define subgroups of patients, using immunologic, biochemical or molecular criteria.

Initially, surface marker assays were used in an attempt at subclassification and, subsequently, these were combined with assays of a number of monoclonal antibodies. It became clear that children with T- or B-cell acute lymphoblastic leukemia invariably had a poorer prognosis than patients classified as non-T, non-B ALL. For some of these children, we instituted bone-marrow transplantation after the first remission. Also we demonstrated the potential of certain drugs against T-cell ALL, particularly arabinosylguanine, which has a selective toxicity to such cells.

To further analyse the heterogeneity of the large number of patients with Ia^+, $CALLA^+$ non-T, non-B ALL, we developed a cellular radioimmunoassay for direct quantitation of numbers of Ia and CALLA sites on these cells. We have studied approximately 50 patients in this way and are following them to determine if the quantitative expression of differing amounts of antigen has prognostic importance.

Over the last two years, we have studied the organization of immunoglobulin and T-cell receptor genes in leukemia. Using gene probes, DNA from more than 100 patients has been analysed. This powerful approach has provided important information concerning leukemia-cell heterogeneity, identification of clonality, monitoring of therapy and, most important, has provided a basis for understanding normal lymphocyte differentiation.

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*Project 397. (Final Report)

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INTERMEDIATE FILAMENT PROTEIN MARKERS IN PEDIATRIC MALIGNANCIES*

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Antibodies to the intermediate filaments, cytokeratin and vimentin, have been used to differentiate pediatric tumors arising from epithelium and mesenchyme respectively[1]. The antibody to cytokeratin was especially useful in the diagnosis of undifferentiated epithelial tumors for which epithelial derivation was difficult to establish on the basis of light or electron microscopy alone[2], and in helping to elucidate the pathogenesis of controversial tumors[3]. In addition to antibodies to intermediate filaments, several other antibodies have been useful in immunohistochemical studies to confirm the cell of origin of poorly differentiated tumors. Antibodies to S100 protein helped to identify such tumors as melanomas, histiocytosis X, and pleomorphic adenomas[4], and antibodies to myoglobin and creatinine kinase helped to identify rhabdomyosarcomas[5]. We have devised a scheme for the appropriate use of these and other antibodies in the immunohistochemical evaluation of microscopic slides of tumors, so as to increase diagnostic precision by the surgical pathologist[4,6].

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*Project 463.

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Ontario Cancer Institute incorporating the Princess Margaret Hospital, Toronto

LEUKEMIA PROGRAM AT THE ONTARIO CANCER INSTITUTE*

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The leukemia program at the Ontario Cancer Institute is a collaboration between clinical and laboratory scientists; its objective is to define cellular or molecular characteristics of leukemic cells and to use this information as the basis for therapeutic innovation.

Blast Cells in Tissue Culture

We now use two tissue culture methods to study blast cells outside the body. The first is a clonogenic assay; in it, single blast cells give rise to colonies in methylcellulose cultures in the presence of one or more growth factors. Cells can be recovered from colonies, and a minority will form secondary colonies on replating. These observations showed that the blast population could be considered as a lineage maintained by stem cells capable of self renewal. However, the majority of the cells in colonies were end cells without extensive growth capacity. Thus, the clonogenic assay detected primarily terminal divisions; self renewal could be seen only by the replating procedure.

The second culture method is new[1]. Dr. Nobuo Nara found that blast cells would grow in suspension culture, provided a high cell density was maintained, and suitable growth factors were provided. Growth was assessed using the clonogenic assay, and could be expressed as increased numbers of blast stem cells. Subcultures were made after 4 to 7 days; growth could be maintained for times that varied from patient to patient. However, in some instances, cells have been in exponential phase for several months, although periods of 3 to 4 weeks are usual. Evidence was obtained that the growth of blast stem cells reflected their renewal capacity. Thus, the suspension assay was complementary to the methylcellulose method; while the latter depended on terminal divisions, the former displayed directly stem-cell self renewal.

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*Project 402.

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Growth Factors

We have begun experiments designed to define growth factors (LBGF) for AML blast cells, in collaboration with scientists at the Genetics Institute in Boston. These workers have prepared expression libraries from cDNA obtained from LBGF-producing cells. Following transfection, cos monkey cells transiently produce proteins encoded by cDNA fragments in the library. By screening cos supernatants, we hope to identify the gene responsible for LBGF.

Lineage Infidelity

In some instances single blast cells can be identified that express simultaneously markers usually associated with more than one lineage. This phenotype has been called 'lineage infidelity', to contrast it with the faithful patterns of differentiation seen in normal lineages. Patients whose blast populations included doubly-marked cells had a poor response to treatment – a clinical observation, which supported the validity of the detection of the lineage infidelity phenotype.

The interpretation of lineage infidelity has been controversial. Some have suggested that the presence of markers of more than one differentiation pathway on single blast cells represents persistence of a phenotype found in the earliest stem cells; its presence in blast cells, then, would provide evidence for their origin by transformation of such stem cells. We have proposed an alternative view; that lineage infidelity is a manifestation of the abnormal gene expression required for a novel blast lineage to be assembled from components of normal differentiation programs.

We have examined the issue further by using methods for detecting components of differentiation programs that do not depend on the recognition of immunologically-defined markers. Dr. Gregory Cheng used hydrocortisone sensitivity as a way of distinguishing between myelopoietic and lymphoid programs. He showed that lymphoid colony-formation was highly and uniformly sensitive to the hormone, while granulopoiesis proceeded uninhibited even in the presence of large hydrocortisone concentrations. When blast progenitors were tested, marked patient-to-patient variation was found. Moreover, there was a significant association between hydrocortisone sensitivity and failure to achieve remission. The findings were interpreted to mean that hydrocortisone-sensitive blasts followed differentiation programs that included lymphoid components; the presence of such components in the programs of AML blasts was considered to be a manifestation of lineage infidelity[2].

Clinical Trials

The laboratory studies of AML blasts have always been closely integrated into clinical trials of chemotherapy. The most recent trial, employing high dose cytosine arabinoside (Ara-C) as a single agent for induction and maintenance, has given an improved response rate compared to previous regimens using multiple drugs. In addition to its general cytotoxic effects, Ara-C was shown to reduce the plating efficiency of blasts obtained from primary colonies. This finding was interpreted to mean that Ara-C inhibits self renewal specifically. Additional support for this view has been obtained using the suspension assay. Growth of clonogenic blasts in suspension was much more sensitive to Ara-C than colony formation in methylcellulose. Further, for a small subgroup of 15 AML patients, in whom Ara-C survival curves were available for cells tested both in suspension and in methylcellulose, there was a significant association between drug sensitivity in suspension, but no such correlation emerged for sensitivity in methylcellulose[3].

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CLINICAL TRIALS SECRETARY FOR GASTROINTESTINAL TUMOR GROUP*

B.J. CUMMINGS** and G. DeBOER†, *Toronto, Ontario*

The funding for this project provides secretarial assistance for studies on patients with gastrointestinal malignancy.

Studies of treatment with combinations of radiation and chemotherapy using 5-fluorouracil and mitomycin C have been continued in patients with anal or esophageal cancer. Primary tumor control rates of 90% for anal cancer and of 60% for esophageal cancer have been maintained.

A pilot study of preoperative radiation for rectal carcinoma has been completed. A randomized trial has now been opened, in collaboration with members of the Department of Surgery at the University of Toronto, and with surgeons in the community. In this trial, the results of surgical resection will be compared with those of resection preceded by 45 Gy in five weeks.

The randomized trial comparing 5-fluorouracil with 5-fluorouracil plus folinic acid for patients with metastatic colorectal carcinoma has continued and accrual is almost complete.

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*Project 427.

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CLINICAL TRIALS IN BREAST CANCER[*]

R.M. CLARK[**], N.F. BOYD[†], U. AMBUS[‡] and
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Four randomized controlled clinical trials are now in progress. These are:

1. A trial of ovarian irradiation and prednisone, following operation and radiotherapy undertaken for carcinoma of the breast, compared three forms of adjuvant therapy: ovarian irradiation and prednisone; ovarian irradiation alone; and no further treatment. The 756 patients, who were enrolled now have been followed for at least eight years. In premenopausal women, aged 45 years or more, ovarian irradiation and prednisone significantly delayed recurrence, and prolonged survival. Further follow-up and analysis continue.
2. A trial is being conducted of postoperative treatment of breast cancer in premenopausal patients with histologically involved axillary nodes. This trial compares two treatments: (a) combination chemotherapy with cyclophosphamide, methorexate and 5-fluorouracil (CMF), and ovarian irradiation plus prednisone; and (b) CMF alone. The trial is designed to determine if chemotherapy and hormonal therapy are complementary. To date 210 patients have been enrolled, but as yet no results are available.
3. A trial was conducted of postoperative treatment of breast cancer in postmenopausal patients with histologically involved axillary nodes. This trial, which used tamoxifen as an adjuvant, was completed in April 1984 with 400 patients enrolled. Overall the four-year, actuarial, relapse-free rates were 48% for patients receiving tamoxifen versus 35% for patients receiving no further treatment. As yet, there is no difference in overall survival between these two groups. Estrogen receptor status was known in 250 patients and progesterone receptor status in 241. Improvement in disease-free survival appeared to be confined to the receptor-positive subgroup. These results suggest that tamoxifen is useful in decreasing the recurrence rate in postmenopausal women with axillary-node-positive breast

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[*] Project 446, including Projects 378 and 386.

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cancer following mastectomy. Benefit appears to be confined to women with receptor-positive breast cancer. Further folllow-up and analysis continue.

4. A Phase II trial studied the value of tamoxifen in the treatment of metastatic breast cancer in premenopausal women. Of 74 evaluable patients, 5 have had complete responses (CR) and 15 have had partial responses (PR). Twelve have remained stable (ST) on treatment. The response rate (27% for CR + PR; 43% for CR + PR + ST) and the response duration (13 months) suggest that tamoxifen may achieve an effect comparable to that of ovarian ablation in premenopausal women with metastatic breast cancer. The study has also shown that generally steroid receptors were predictive of response to tamoxifen, and that tamoxifen response was highly predictive of response to subsequent ovarian ablation.

SURVEILLANCE ALONE IN THE MANAGEMENT OF CLINICAL STAGE I NON-SEMINOMATOUS TESTICULAR CANCER*

J.F.G. STURGEON** and J.G. HERMAN†, *Toronto, Ontario*

A prospective cohort of patients believed to have clinical Stage I non-seminomatous testicular cancer, were followed with no treatment after orchidectomy. We wished to establish the proportion of patients whose disease would progress while on surveillance, the time from diagnosis to clinically apparent disease, the anatomical sites of disease, and also to learn whether treatment delayed until the time progression became apparent would result in cure of disease.

Since it began in January 1981, 52 patients have been entered on this study and 40 patients now have been followed for longer than one year. Patients with disease progression shown by elevated tumor markers alone, pulmonary metastases, or extra-abdominal disease received chemotherapy for three months, using a regimen including bleomycin, actinomycin-D, vinblastine and cis-platinum. All other patients with progression now undergo a retroperitoneal lymph-node dissection, although at the beginning of the study, patients with retroperitoneal disease and elevated tumor markers received radiation to the retroperitoneum.

We have observed progression in 19/40 patients (47.5%), and it occurred from 2 to 21 months after diagnosis (median time 6 months). Tumor markers were elevated at the time of progression in 17/19 patients. Progression occurred in 8/13 (62%) patients with embryonal carcinoma, 10/17 (58.7%) patients with teratocarcinoma, and in 1/10 (10%) patients with immature teratoma. Fourteen patients had progression in the retroperitoneum, revealed by CT scan; two demonstrated lung metastases, and three had persistent marker elevation only.

Of 19 patients requiring regional or systemic treatment, 18 are alive from 3 to 48.5 months (median 18 months) after completing all therapy; one patient died of his disease, 24 months from diagnosis, after refusing further treatment.

These results suggest that a policy of surveillance for clinical Stage I patients may spare at least 50% of them from the morbidity of earlier and unnecessary treatment. Moreover, if treatment is given only when clinical disease is apparent, almost all patients will be successfully salvaged. The interpretation of the initial CT scan and lymphogram are critical in determining whether patients proceed to surveillance or immediate treatment. We believe that a policy of surveillance should be considered only for patients who will be reliable for follow-up, and when management will be the responsibility of physicians experienced in the diagnosis and treatment of this disease.

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*Project 447.

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CHARACTERIZATION OF CULTURE-INDUCED CYTOTOXICITY FROM HUMAN PERIPHERAL LYMPHOID CELL SUBPOPULATION*

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Preliminary experiments demonstrated the generation of cytotoxicity by high-density lymphoid cells of human peripheral blood origin after short-term culture in a medium containing fetal-calf serum[1]. We sought to characterize the physical and functional attributes of effector and precursor cells. Using a Percoll discontinuous-density-gradient technique, maximal culture-induced cytotoxicity (CIC) was detectable after two or three days in culture. Some CIC was generated by lower density cells, which evolved among a higher density subpopulation. By removing surface marker -- specific cells with different monoclonal antibodies using a "panning" technique, we have shown that cells required to generate CIC and their precursor cells lack the natural killer (NK) cell associated HNK-1 and OKT3 antigens but display the OKM1 antigen. It appeared that cells possessing the OKT3 antigen had a suppressive effect on CIC. Using other tumor cell lines, we found that CIC was generated against two of three teratocarcinoma cell lines and an NK-resistant cell line[2]. Thus, this subset of lymphoid cells is distinct from lymphokine (IL-2) activated killer cells[3] and natural killer cells. Differential cytotoxicity against different teratocarcinoma cell lines may be related to varying expression of recognition structures or degree of differentiation.

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*Project 468.

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ADDITIONAL INVESTIGATIONS

Dr. R.D.T. Jenkin, Director of the Toronto-Bayview Regional Cancer Centre, reports on the following clinical research investigations:

CO-OPERATIVE CLINICAL TRIALS

Dr. I.G. Kerr has entered patients into several NCIC clinical trials. These include Phase II studies of NMF (colorectal, glioma, melanoma) and carboplatinum (ovary).

INTRAPERITONEAL CHEMOTHERAPY

Dr. I.G. Kerr has continued a high-volume intraperitoneal chemotherapy program. Two trials have been closed (5-FU, aclarubicin) and two new trials for palliation of malignant ascites and consolidation treatment of ovarian cancer are being developed.

EFFECT OF PATIENT AGE ON THE CLINICAL PHARAMCOLOGY OF ANTICANCER DRUGS

Dr. I.G. Kerr is continuing a study looking at the relationship between patient age and toxicity and pharmacokinetics of 5-FU in patients with colorectal cancer, funded by NCIC.

AMBULATORY INFUSION PUMP PROGRAM

Drs. I.G. Kerr and N. Iscoe have continued their ambulatory I.V. infusion pump program, predominantly in patients with colorectal cancer. Further Phase I-II trials are being planned.

MICROCOMPUTER-ASSISTED FILM DOSIMETRY

Mr. P.F. O'Brien has directed a summer student in the development of computer software and interface hardware to produce a computer driven film dosimetry system. For the scanned electron beams on the Therac 25, x-ray film is the most convenient method of measuring isodose distributions. With the system developed in the Clinical Physics Division, a densitometer is scanned over the film in a user selected grid pattern. Scanning is computer controlled and resulting density values are stored as files on a floppy disk. Measured film response data are used to convert the density values to absorbed dose and the required isodose curves are interpolated from the stored grid. The isodose pattern is stored and may be displayed on the CRT or on a printer.

OXYGEN DEPLETION IN IRRADIATED AQUEOUS SOLUTIONS CONTAINING ELECTRON AFFINIC HYPOXIC CELL RADIATION SENSITIZERS

Dr. H.B. Michaels is continuing his studies to investigate the mechanism of radiolytic oxygen depletion and the interference with this process by radiosensitizers at low levels of oxygen in aqueous solutions and in mammalian cells. The yield of oxygen depletion, monitored continuously during irradiation with a sensitive oxygen electrode, is measured in sealed solutions of tissue culture medium containing sensitizers. Various nitroimidazole and nitrofuran drugs are being tested, including misonidazole and metronidazole. The experimental data are being used in the development of a model to explain the radiation chemical interaction of sensitizer and oxygen depletion in cells.

COMMISSIONING OF THE SECOND THERAC 25

Dr. R.A. Siwek, Mr. P.O'Brien, Dr. H. Michaels and Mr. B. Gillies carried out radiation protection measurements on the second Therac 25 linear accelerator. Radiation beam characteristics of the photon and electron modes were measured.

BRACHYTHERAPY DOSIMETRY

Dr. R.A. Siwek is carrying out brachytherapy dosimetry to standardize source loadings for Fletcher-type applicators, ovoids and single line sources. The use of the Selectron remote afterloading unit (for radioactive cesium-137 implants) is being extended further for treatment of the esophagus. A sealed source, iridium-192, has been employed recently in the treatment of the chest wall and vulva. In the near future, iodine-125 seeds are to be used for treatment of the prostate.

PHYSICAL ASPECTS OF HIGH ENERGY PHOTON BEAMS IN LOW DENSITY MATERIAL

Measurements are being taken by Mr. P.F. O'Brien to determine the dose distribution in low density material and at the interface between low density material and unit density material, for high energy photon beams. Electron transport effects significantly alter the distributions in these regions. Current treatment planning algorithms do not correct for these effects. The aim of this project is to determine the size of the effect and to identify those treatment techniques for which this problem may be important.

MICROCOMPUTER-ASSISTED, PATIENT-CONTOUR TAKING DEVICE AND COMPENSATOR DESIGNING APPARATUS

The contour taking device is now being used routinely for taking patient contours. The device enables the dosimetrist to obtain information in all of the required planes with an accuracy of ±2 mm. Efforts of the clinical physics staff are now being directed towards transferring contour information directly to the treatment planning computer and also to the development of software for the design of compensators for missing tissue and field shape.

STUDY OF THE LEU-7 ANTIGEN

Dr. J.J. Rusthoven of the Toronto-Bayview Centre and Dr. Susan Cole of the Kingston Centre have previously reported that the monoclonal antibody Leu-7 reacts with small-cell lung carcinoma cells, prostate epithelium and, at least, some prostate carcinomas. Using immunoisolation techniques, they are working to characterize the antigen(s) and epitope(s) responsible for this reactivity. In addition, they are testing tumor tissue from patients with prostate and lung carcinoma for the presence of this reactivity. Ultimately they hope to determine whether Leu-7 can be used to detect metastatic disease involving these tumor types.

University of Toronto

STUDIES IN ADULT LEUKEMIA*

M.A. BAKER**, *Toronto, Ontario*

Clinical Studies

The Toronto Leukemia Study Group has reviewed 272 adult patients with acute myeloblastic leukemia admitted to the 14 hospitals in the group over a seven-year period. We found that 43 patients were untreated, usually at the discretion of the attending physician, that 31 patients did not complete a full course of therapy, and that 198 patients were fully treated. There were 79 patients aged 70 or over, 34 with preceding myelodysplastic syndrome, and 18 with pre-existing malignant disease or cytoxic chemotherapy. If all patients, treated or untreated, were included in the analysis, the complete remission rate was 43%. Exclusion of untreated, partially treated and high-risk patients from the analysis would raise the apparent remission rate to 85%. Thus, reports of the results achieved in leukemia treatment must be interpreted in the light of how many patients were excluded from the various categories.

A randomized study of 125 patients in complete remission examined the efficacy of remission maintenance and the effect of early treatment in adult patients with acute myeloblastic leukemia. Patients were induced with cytosine arabinoside, daunorubicin and 6-thioguanine and given four months consolidation therapy with the same drugs. Patients in arm A received continuing maintenance therapy, those in arm B had no further chemotherapy until relapse, and those in arm C received reinduction chemotherapy when immunodiagnostic studies of bone marrow showed evidence of imminent relapse. There was no significant difference in survival among the three arms suggesting that remission maintenance is not warranted in this regimen. Early retreatment of unmaintained patients with current drugs does not prolong survival.

Laboratory Studies

Granulocytes from patients with chronic myelogenous leukemia (CML) show pathophysiological abnormalities, which are reversed by treatment of the cells with neuraminidase. Studies with selective lectins and biochemical analysis of membrane glycoproteins support the suggestion that the abnormal behavior is due to aberrant sialylation of the leukemic granulocytes. Recently we have shown that the changes in physiology and the accompanying changes in sialylation are reversed in part by chemotherapy given for this disease. Also we have documented an abnormality in a sialyltransferase which appears to be responsible for the sialylation defect. In CML, the sialyltransferase, which specifically sialylates O-linked Gal-GalNAc, shows a several-fold increase in activity. Further studies of the mechanism of enzyme activation are in progress.

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*RA-200.

**OCTRF Research Associate; and Professor of Medicine, University of Toronto.

RETINOBLASTOMA: A MODEL OF ONCOGENESIS*

B.L. GALLIE**, *Toronto, Ontario*

Retinoblastoma (RB), a rare tumor of the eye, provides a prototype for childhood malignancy in general. Over the last few years we have shown that RB tumors arise because of mutations in both copies of a specific gene on chromosome 13[1]. A mutation in only one copy of this gene has no effect, but when carried in the germ line and all constitutional cells of an individual, it predisposes to malignant tumors. The tumors, which include RB and osteosarcoma, arise when the remaining normal copy of the RB gene is lost by variety of mechanisms[2,3]. Laboratory studies show that the cell of origin for RB is a primitive neuroectodermal cell which can further differentiate in response to changes in the microenvironment[4]. Since these cells normally lose all proliferative potential in fetal life, we suspect that the normal action of the RB gene is to control proliferation or initiate terminal differentiation in specific types of cells.

By the time RB tumor cells can be examined in the laboratory, they have acquired additional genetic changes. Most of the tumors tested[5], contained one of two specific chromosomal rearrangements but these have not been linked to abnormal expression of any known oncogene. Two of the RB tumors that grow best in the laboratory have developed amplified copies of the oncogene N-myc. All other RB tumors, however, express N-myc at a similar level to fetal retina.

Retinoblastoma is a good model by which to study the earliest steps in oncogenesis, because we know the location of the initiating gene. Current work is directed toward defining the characteristics of the cell of origin and isolating the RB gene.

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*RA-202.

**Associate Professor of Ophthalmology, University of Toronto; and OCTRF Research Associate.

THE RELATIONSHIP OF PHEOMELANIN AND ULTRAVIOLET RADIATION IN CARCINOGENESIS*

H.F. HABERMAN** and I.A. MENON†, *Toronto, Ontario*

The relationship of skin color and cutaneous carcinogenesis is being studied in a group of patients treated with psoralen and ultraviolet light A (PUVA) for psoriasis and vitilago, and in a group of renal transplant patients.

Pheomelanin, the melanin found in people with light-colored and freckled skin, differs chemically and biologically from eumalanin, that found in dark-colored people. Our studies have shown that these two melanins have diferent physical, chemical and biological properties. Especially, irradiation of pheomelanin produces superoxide, hydrogen peroxide and enhanced free radical contents; irradiation of this melanin with cells produces cytotoxic reactions, e.g. cell lysis, ultrastructural changes in the cellular components, lesions in the DNA, release of histamine etc. These photobiological properties of pheomelanins are due to the superoxide and hydrogen peroxide formed and to the increased free-radical contents of the melanin induced by the irradiation. These findings suggest that the presence of pheomelanin might contribute positively to the aging and carcinogenesis in the skin induced by ultraviolet radiation.

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*RA-203.

**OCTRF Research Associate; Head of Dermatology, Toronto Western Hospital; and Associate Professor of Medicine, University of Toronto.

†Biochemist, Department of Medicine, U of T.

EVALUATION OF A NUCLEAR ESTROGEN RECEPTOR ASSAY FOR HUMAN BREAST CARCINOMA*

G.E. MOBBS**, *Toronto, Ontario*

This project will examine the possibility of replacing the conventional radioligand assays for estrogen and progesterone receptor (ER and PgR) with a modification of a recently available commercial kit for ER assay. This uses monoclonal antibody to ER in a solid-phase enzymeimmunoassay (EIA), and, unlike the conventional assays, is quick and relatively easy to perform, requires no expensive equipment, and is fully standardized. However, like the conventional ER assay, it is designed to quantitate cytosolic ER (ERC) only, and the advantages of the EIA method are greatly diminished because one must continue to measure PgR by the radioligand assay. The reason for quantitating PgR is to provide an indicator of the functional activity of ER in the tumor tissue; however, a number of studies suggest that presence of nuclear ER (ERN) may be strongly related to the presence of cytosolic PgR (PgRC), and may provide an equally good indicator of ER function and hormonal sensitivity. If the EIA assay could be adapted to the assay of ERN, it might be possible to replace both radioligand assays with a single ERN assay. We have established that the ER-EIA can be carried out under the conditions necessary for the extraction of ERN. To date, we have carried out cytosol and nuclear ER-EIA on 25 breast carcinoma specimens, and have related the results to the ERC and PgRC concentrations assayed by the conventional radioligand (DCC) assay. Even in this small preliminary series, we observed significant linear correlations between log PgRC and both log ERN ($r=0.60$, $P<0.01$) and log ERC ($r=0.49$, $p=0.02$). Moreover, in 78% of the tumors, positivity or negativity for PgRC was associated with high and low concentrations (above and below 150 fm/mg DNA) of ERN respectively. Further work will determine whether PgRC is more closely related to ERN than to ERC, and which parameter is the best prognostic factor and predictor of hormonal sensitivity.

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*RA-205.

**OCTRF Research Associate; and Associate Professor of Surgery (Research), University of Toronto.

HORMONE RECEPTOR MECHANISMS IN THE DEVELOPMENT AND TREATMENT OF PROSTATIC NEOPLASIA*

G.E. MOBBS**, *Toronto, Ontario*

Considerable circumstantial evidence suggests that endogenous estrogen may be involved in the development of prostatic disease, but no one has demonstrated the mechanism of such an effect. If the prostate is a direct target organ for estrogen, one would expect it to contain estrogen receptor protein (ER), and to find that estrogen treatment would induce the synthesis of progesterone receptor protein (PgR). Using the R3327 (Dunning) prostatic carcinoma in the rat, we have investigated the control and quantitative relationship between cytosol and nuclear ER and PgR in tumors treated with diethylstilbestrol (DES) and the antiestrogen tamoxifen. The receptor proteins responded to these treatments in the same way as in female estrogen target organs. We are now investigating the possibility of using DES-induced PgR in the prostate tumors as a target for a cytotoxic drug conjugated with progesterone.

We have also examined the androgen receptor (AR), nuclear ER and cytosol PgR content of 23 specimens of human benign prostatic hyperplasia (BPH), 8 specimens of prostatic carcinoma, and 5 "normal" prostates obtained from young kidney donors, to investigate possible differences in hormone-receptor profile between normal and neoplastic human prostates. Since BPH and carcinoma arise in different regions of the prostate, we examined regional receptor profiles in the normal specimens whenever possible. Mean AR and PgR concentrations were lower in the normal than in the BPH specimens but, paradoxically, nuclear ER was detected in 3/5 of the normal prostates, and in only 2/23 BPH specimens. No consistent regional differences in receptor profile were observed in the normal specimens. No nuclear ER was detected in the carcinoma specimens, and AR and cytosol PgR concentrations were much more variable than in the BPH specimens. It will be of great interest to see whether estrogen treatment has the same effect on human carcinoma as in the rat model, i.e., whether nuclear-associated ER becomes detectable, and cytosol PgR concentrations increase.

This project was supported by NCIC.

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*RA-205-1.

**OCTRF Research Associate; and Associate Professor of Surgery (Research), University of Toronto.

RESEARCH UNIT OF THE DIVISION OF EPIDEMIOLOGY AND STATISTICS OF THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION*

E.A. CLARKE**, N. KREIGER† and L.D. MARRETT‡
Toronto, Ontario

This Unit has been affiliated with the Department of Preventive Medicine and Biostatistics, University of Toronto, since 1978. It was established to conduct analyses using the cancer-data bases of the OCTRF, to assess the quality of these data, to co-operate with cancer researchers by providing epidemiological and biostatistical assistance, to conduct or support cancer research projects, and to provide information which will improve the knowledge of the general public and scientific community.

The following members of the Unit hold academic appointments at the University: Drs. E. Aileen Clarke, Loraine D. Marrett, and Nancy Kreiger. We continue to collaborate with the International Agency for Research on Cancer in studies of second primary cancers. The data collection phase of a case-control study of second primary cancers associated with radiation for cervical cancer has been completed and analysis will be undertaken in 1986. We have completed a cohort analysis of second primaries occurring in individuals diagnosed with Hodgkin's disease, testicular cancer, and ovarian cancer between 1964 and 1982. We found the anticipated excess of leukemia in common with other registries. The results of all nine cancer registries suggested an excess of non-Hodgkin's lymphoma and connective tissue tumors -- a finding which merits further investigation.

Analysis of 50 years of cancer mortality data for Ontario continues, including age-period-cohort modelling and assessment of the effects of therapy. Recently, we did a special study of testicular cancer mortality in the province between 1964 and 1982 to determine trends in seminomatous and non-seminomatous testicular cancer, separately, over a period of dramatic therapeutic advances. In addition, the Unit is conducting population-based survival studies of Hodgkin's disease and testicular cancer by histologic cell type and other factors.

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*Project 381.

**Head, Division of Epidemiology and Statistics, Ontario Cancer Treatment and Research Foundation, Toronto; and Associate Professor in the Department of Preventive Medicine and Biostatistics, University of Toronto.

†Head of Statistics, OCTRF; and Assistant Professor in the Department of Preventive Medicine and Biostatistics, U of T.

‡Epidemiologist, OCTRF; Assistant Professor in the Department of Preventive Medicine and Biostatistics, U of T; and Assistant Professor of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton.

Dr. Clarke is collaborating with Dr. Stephen Walter at McMaster University in Hamilton in an evaluation of cervical cancer and dysplasia screening programs. Dr. Clarke also participated in a collaborative study conducted under the aegis of the International Agency for Research on Cancer, to estimate the risk of invasive cancer associated with different screening intervals.

Dr. Clarke also has been studying the relationship between oral contraceptive use and cervical neoplasia, with particular emphasis on issues of bias and confounding. She is collaborating with the Boston Drug Epidemiology Unit in a multicentre case-control study of breast cancer, focussing on the roles of diazepam and alcohol as risk factors. These latter data also are being used with information from the Ontario Cancer Registry to investigate risk factors associated with estrogen receptor status in women with breast cancer.

Dr. Marrett has continued to oversee the Toronto component of a case-control study of malignant melanoma, being conducted collaboratively between McMaster University, the University of Toronto and the OCTRF. In addition, she is analyzing data from Connecticut, including an investigation of bladder cancer and leather worker, the occurrence of bladder cancer in a cohort of benzidine-exposed employees, and the association between lower urinary tract tumors and analgesic use.

In collaboration with Dr. W.E. Rawls of McMaster University, Dr. Marrett has been investigating the relationships between cervical cancer, Herpes simplex virus type 2, and sexual risk factors for cervical cancer. She also is acting as a consultant to the DES (diethylstilbestrol) Registry, which is being established at the Wellesley Hospital in Toronto.

Dr. Kreiger is completing her study of the epidemiology of fracture in postmenopausal women, funded by Health and Welfare Canada, and is continuing to develop a proposal for an epidemiological study of risk factors for osteogenic sarcoma in children and young adults.

In collaboration with the City of Toronto Department of Public Health, Dr. Kreiger is involved with the design, data collection, and analysis of an historical cohort study of an industrial-residential neighbourhood. This study is using the Ontario Cancer Registry for cohort follow-up.

Dr. Kreiger and co-workers in the Unit have completed the analysis of a case-control study of endometrial hyperplasia, which is scheduled to be published in the American Journal of Epidemiology.

Windsor Regional Cancer Centre

CLINICAL INVESTIGATIONS

Dr. G.K. Mok, Director of the Windsor Regional Cancer Centre, reports on the following clinical research investigations:

NATIONAL CANCER INSTITUTE OF CANADA

The Windsor Group participates in many of the national trials including the following:

- Early versus late radiotherapy in the treatment of limited small-cell carcinoma of the lung.
- Adjuvant treatment of primary breast cancer (Stage II) in postmenopausal patients.
- The comparison of cyclophosphamide and cis-platinum versus cyclophosphamide and carboplatin in the treatment of ovarian carcinoma with macroscopic residual disease.
- Clinical trial of MOPP/ABV hybrid versus alternating MOPP/ABVD for advanced or recurrent Hodgkin's disease.
- A comparison of standard BACOP with escalated BACOP in patients with poor prognosis non-Hodgkin's lymphoma.

ONTARIO CLINICAL ONCOLOGY GROUP (OCOG)

The clinicians continue to contribute patients to OCOG: first, to the prospective randomized clinical trial to assess the effectiveness of breast radiation following partial mastectomy and axillary dissection for carcinoma of the breast in node-negative patients; and second, to the randomized control trial comparing 12 weeks with 36 weeks of adjuvant chemotherapy for operable high-risk breast carcinoma.

ADVANCED BREAST CANCER IN CO-OPERATON WITH LEDERLE CORP.

The Windsor Centre is continuing a randomized trial comparing the effectiveness of single agent Novantrone (DHAD) to standard CMF chemotherapy as first-line treatment in relapsing breast cancer. This crossover trial includes both positive and negative estrogen-receptor tumors but excludes patients with liver metastases.

SOUTHWEST ONCOLOGY GROUP (SWOG)

The medical oncologists at the Windsor Centre, as associate members of Wayne State University, actively supported the SWOG program, both in patient entry to protocols and by active participation in brain and gastrointestinal committees. This participation introduces promising new agents and treatment modalities to upgrade the skills and services availabe in the Windsor area. The principal investigators are the medical oncologists, Drs. D.B. McDonald, H.T. Abu-Zahra and S.S. Yoshida, while the radiation oncologists, Drs. G. Mok and C. Springer, provide the radiation therapy portion of the protocols.

EPIDEMIOLOGY AND STATISTICS

CANCER INCIDENCE, MORTALITY AND TREATMENT IN ONTARIO

E.A. CLARKE, M.B., B.S., M.Sc.* N. KREIGER, M.P.H., Ph.D**
and L.D. MARRETT, Ph.D** *Toronto, Ontario*

The Division of Epidemiology and Statistics is responsible for the adequate reporting of cases and the recording and compilation of data: One of the mandates of the Foundation under the Cancer Act. In pursuit of these objectives, the Foundation has maintained and improved a uniform case-recording system, which was adopted by the regional cancer centres in 1947, and by the Ontario Cancer Institute incorporating the Princess Margaret Hospital (OCI/PMH) in 1957. The data from the regional cancer centres and the OCI/PMH are in machine-readable form from 1960 onwards. In addition to these records, the Foundation's computerized cancer-data base contains individual records on residents of Ontario who died from cancer since 1950; tabulations of deaths by sex, five-year age groups, and type of cancer from 1931 to 1984; individual records of patients diagnosed as having cancer in the Province between 1964 and 1983; individual records of hospital discharges on patients with cancer from 1964 to 1984; and pathology reports on specimens with cancer from 1972 to 1984. The total volume of records, in excess of three million, provides the Division with a unique opportunity for descriptive cancer epidemiology and allows the Division to assist other cancer researchers in the investigation of possible carcinogenic effects of exposure to occupational and environmental agents.

Most of the staff of the Division are located in the Head Office at 7 Overlea Blvd., but the Epidemiology Research Unit of the Division is located in the Department of Preventive Medicine and Biostatistics at the University of Toronto. Drs. Clarke, Kreiger and Marrett have cross-appointments in that department. This arrangement allows the staff of the Division to interact with other members of the epidemiological community and with medical and oncological colleagues.

In addition to the analyses of cancer incidence and mortality in the Province, the staff of the Division are involved in a number of other projects. Some are collaborative, using Ontario Cancer Registry data, with such agencies as the International Agency for Research, and the National Cancer Institute. Other studies are field studies conducted principally out of the Epidemiology Research Unit. Most of the case-control studies are supported by peer-reviewed grants.

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**Epidemiologist, Division of Epidemiology and Statistics, OCTRF.

CANCER INCIDENCE AND MORTALITY

The Ontario Cancer Registry

In December 1985, the Ontario Cancer Registry produced 20 years of incidence data for the Province. The Registry now comprises information on more than 500,000 cases of cancer newly diagnosed in residents of Ontario between 1964 and 1983.

The Ontario Cancer Registry employs a unique system of registration, based on computerized record linkage on cancer cases collected routinely for other purposes and provided to the Foundation. The Registry receives more than 200,000 such records annually. The following province-wide data are routinely forwarded to the Registry:

1. Hospital discharges with a mention of cancer collected by the Hospital Medical Records Institute (HMRI) and supplied by the Ontario Ministry of Health; 100,000 computerized records per year.
2. Pathology reports with a mention of cancer submitted voluntarily by hospital pathology laboratories; about 35,000 paper records per year.
3. Reports on patients referred to the regional cancer centres and the OCI/PMH; 20,000 computerized records per year.
4. Deaths from all causes supplied by the Registrar General of Ontario; 65,000 computerized records per year.

Once source files are preprocessed, cancer incidence data are created in two major phases. First, sequential computer linkage of the source files is carried out to bring all records pertaining to an individual together. Then, a set of computerized rules called "case resolution" is applied to the linked records, to determine site of disease, histology, and date and method of diagnosis. Manual resolution of problems arising as a result of either linkage or case resolution is routine.

To link together the large volume of data, the Foundation staff have developed a sophisticated computer record linkage system based on the Generalized Iterative Record Linkage System (GIRLS), designed by Statistics Canada in conjunction with the Epidemiology Unit of the National Cancer Institute of Canada. This system and the sequence of linkages is described in more detail in Information Systems section.

"Case resolution" consists of a set of computer programs, developed by Foundation staff, which apply medical logic to determine the appropriate site of disease, histology, and date of diagnosis. Cases may be supported by one or many source records: Some cases may have only a pathology report or a death certificate; some may have several hospital discharges, several pathology reports, and several treatment centre reports. Obviously, the number of sources of records contributing to a case will determine the quantity and quality of data available on that cancer diagnosis.

The generation of incidence data for Ontario by the Foundation is a joint effort between the staffs of the Division of Epidemiology and Statistics and Information Systems, who together have developed these systems of record linkage and case resolution.

All incidence data presented are given according to the International Classification of Diseases, Ninth Revision (ICD9). While the Registry originally had coded the cancer sites according to the Eighth Revision between 1964 and 1978, all records now have been converted to ICD9.

Cancer Incidence and Mortality, 1983

Currently the time lag between cancer diagnosis and publication of incidence data by the Ontario Cancer Registry is about two years. There is a delay until the essential data have been provided by the sources, then it is necessary to code pathology reports, edit and process the files as described. Thus, the most recent cancer incidence data are for 1983; these are presented in Tables I through IV and Fig. 1. Although last year's report gave cancer mortality data for 1983, we show them again in Tables III and IV, and Fig. 1, to facilitate comparisons between incidence and mortality for the same year.

Tables I and II give the frequencies by 5-year age group for each cancer site or group of sites, for males and females respectively for 1983. Rank order is given in the far right-hand column to aid in quick identification of sites of most frequent occurrence. Cancer of the cervix is overreported in 1983 by about 10% because, in error, we reported some cases of non-invasive disease; this will be identified and corrected later in 1986. Fig. 1 indicates the frequencies of cancer in selected sites and causes of death for both sexes in 1983. We have included the 10 most common sites, in terms of their sex-specific incidence frequencies; they are ordered according to their sex-specific incidence frequencies.

Tables III and IV present incidence and mortality rates by age group and site for males and females respectively for 1983. The rates for 15-year age groups and for all ages are age-adjusted, using the World Standard Population shown in Table VII. Description of the method of direct age-adjustment used here can be found in *Cancer Incidence in Five Continents*, vol. 4, by Waterhouse et al. Rates in the table have been "age-adjusted" to assist comparisons between the different areas. Adjustment for age is used to account for differences caused solely by differences in the age distribution in these areas. The rates shown in Tables III and IV can be compared with any other rates covering the same age span and using the same standard population for adjustment.

The "cumulative risk" (0-74), shown in the final column, is described in detail in *Cancer Incidence in Five Continents*. It is expressed per 100 and is a reasonable approximation to the risk to age 74 of being diagnosed or dying with the given cancer. Thus, if the current age-specific rates for female lung cancer were to remain unchanged throughout her life, a girl born in 1983 would have about a 3% chance of

TABLE I

Annual Number of New Cases of Malignant Neoplasms in Males, by Site of Disease and Age at Diagnosis, Ontario 1983

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DEATH (YEARS)																		RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Age Unknown	All Ages	
Lip and oral cavity	140-145	0	0	0	2	2	2	10	8	16	28	51	71	66	92	70	103	7	528	8
Pharynx	146-148	1	0	0	0	1	0	0	4	8	16	24	27	35	24	16	16	0	172	
Esophagus	150	0	0	0	0	0	0	0	1	6	8	15	18	41	41	39	50	0	219	
Stomach	151	0	0	0	0	0	3	1	14	12	21	43	56	106	87	91	183	1	618	6
Intestine, except rectum	152,153	1	0	0	0	1	5	16	22	20	46	105	157	225	251	300	485	7	1,641	3
Rectum and anus	154	1	0	0	0	0	2	3	8	10	20	48	99	107	132	117	208	4	759	5
Pancreas	157	0	0	0	0	0	1	4	1	11	16	26	49	86	69	82	121	0	466	9
Nasal cavities, middle ear and accessory sinuses	160	0	0	0	0	0	1	1	2	0	2	3	2	7	5	7	8	0	38	
Larynx	161	0	0	0	0	0	0	0	4	9	24	37	53	64	55	62	44	1	353	
Trachea, bronchus and lung	162	0	0	0	1	2	1	11	13	49	112	243	449	590	621	571	756	4	3.423	1
Bone	170	1	2	7	9	6	5	3	0	4	6	3	6	5	7	3	5	0	72	
Connective tissue	171	5	1	2	6	9	9	4	10	5	5	12	16	15	16	16	24	0	155	
Malignant melanoma of skin	172	0	2	0	4	8	15	21	32	25	24	52	50	39	47	34	42	4	399	
Prostate	185	0	0	0	0	0	0	1	0	2	8	46	121	270	402	532	1.064	3	2.449	2
Testis	186	1	1	1	5	32	40	28	24	14	14	11	2	4	2	4	8	0	191	
Bladder	188	1	0	0	1	3	6	7	18	22	46	58	127	162	192	215	330	6	1.194	4
Kidney and other urinary	189	7	2	0	0	0	0	3	4	18	32	36	65	65	55	62	76	2	427	10
Brain and other nervous system	191,192	7	25	8	18	10	13	13	15	25	25	29	40	52	36	43	46	0	405	
Thyroid gland	193	0	0	0	1	2	2	8	6	4	5	8	8	7	12	7	4	0	74	
Lymphosarcoma and reticulosarcoma	200	2	1	0	6	4	3	5	9	7	17	29	37	44	37	40	65	1	307	
Hodgkin's disease	201	0	5	10	15	26	25	11	20	9	6	5	14	13	8	7	9	1	184	
Other lymphomas	202	3	1	2	2	4	5	9	12	15	18	28	31	30	28	34	47	2	271	
Multiple myeloma	203	0	0	0	0	0	0	0	2	0	6	18	21	26	41	46	80	1	241	
Leukemia	204-208	24	21	9	10	9	9	16	13	16	21	25	39	69	69	82	148	5	585	7
Other and non-specific	Residual	19	5	6	1	13	8	12	11	25	40	78	160	186	179	163	339	8	1.253	
TOTAL	140-208[3]	73	66	45	81	132	155	187	253	332	566	1.033	1.718	2.314	2.508	2.643	4.261	57	16.424	

[1] ICD9 International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
[2] Rank order for 10 most common sites (or site groups).
[3] Excluding non-melanotic skin cancers (ICD9 number 173).

TABLE II

Annual Number of New Cases of Malignant Neoplasms in Females by Site of Disease and Age at Diagnosis, Ontario 1983

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DIAGNOSIS (YEARS)																		RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Age Unknown	All Ages	
Lip and oral cavity	140-145	1	0	0	3	4	6	4	4	3	9	20	27	26	38	28	55	4	232	
Pharynx	146-148	0	1	0	2	0	1	1	1	4	6	6	17	8	6	10	9	0	72	
Esophagus	150	0	0	0	0	0	0	0	0	2	5	5	10	8	12	19	43	0	104	
Stomach	151	0	0	0	1	0	2	4	2	8	23	13	32	36	44	53	193	1	412	
Intestine, except rectum	152,153	0	0	0	4	4	5	8	18	41	53	102	154	213	235	303	744	6	1,890	2
Rectum and anus	154	0	0	0	0	1	4	5	6	11	26	51	42	68	82	82	211	3	592	6
Pancreas	157	0	0	0	0	0	0	1	2	5	13	21	29	41	56	78	145	0	391	
Nasal cavities, middle ear and accessory sinuses	160	1	0	0	0	1	0	1	0	1	1	0	5	0	3	3	7	0	23	
Larynx	161	0	0	0	0	0	0	1	2	2	4	7	5	13	8	4	7	1	54	
Trachea, bronchus and lung	162	0	0	0	3	4	4	5	10	46	66	135	210	224	225	224	254	6	1,416	3
Bone	170	3	3	8	5	4	6	1	3	0	1	2	0	4	7	5	7	0	59	
Connective tissue	171	1	1	4	5	4	5	8	7	2	11	9	9	10	11	12	37	2	138	
Malignant melanoma of skin	172	2	0	2	9	6	30	42	53	32	44	50	49	36	34	26	47	9	471	9
Breast	174	0	0	0	0	4	23	80	175	264	357	424	529	550	463	464	820	13	4,166	1
Cervix uteri	180	0	0	0	1	13	29	55	56	37	45	33	49	48	52	30	50	2	500[4]	7
Body of uterus	182	0	0	0	0	1	6	7	23	25	57	91	164	196	184	144	143	2	1,043	4
Other and unspecified uterus	179,181	0	0	0	1	0	0	3	1	6	3	8	4	2	1	2	13	0	44	
Ovary and fallopian tube	183	0	0	1	4	14	19	18	26	34	53	62	83	82	67	82	116	1	662	5
Bladder	188	0	0	0	0	3	0	0	7	7	14	41	40	42	56	72	154	0	436	10
Kidney and other urinary	189	8	3	0	0	2	0	3	5	8	12	19	27	23	37	40	70	0	257	
Brain and other nervous system	191,192	10	11	19	7	6	9	10	13	18	13	21	39	41	24	26	35	0	302	
Thyroid gland	193	0	0	4	4	19	16	30	23	17	17	13	22	13	10	17	20	2	227	
Lymphosarcoma and reticulosarcoma	200	0	1	1	2	3	3	10	7	10	11	15	33	25	30	33	74	0	258	
Hodgkin's disease	201	0	1	2	9	15	18	12	11	2	7	3	7	6	6	7	7	0	113	
Other lymphomas	202	1	1	1	1	3	4	9	11	9	10	25	28	30	25	29	46	1	234	
Multiple myeloma	203	0	0	0	0	0	0	0	1	4	4	13	11	22	25	44	70	1	195	
Leukemia	204-208	20	13	3	11	7	20	12	10	13	11	15	32	44	60	56	149	4	480	8
Other and non-specific	Residual	14	1	0	4	6	11	7	21	21	40	69	99	122	146	161	501	5	1,228	
TOTAL	140-208[3]	61	36	45	76	124	221	337	498	632	916	1,273	1,756	1,933	1,947	2,054	4,027	63	15,999	

[1] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
[2] Rank order for 10 most common sites (or site groups).
[3] Excluding non-melanotic skin cancers (ICD9 number 173).
[4] Approximately 10% non-invasive cancer of the cervix.

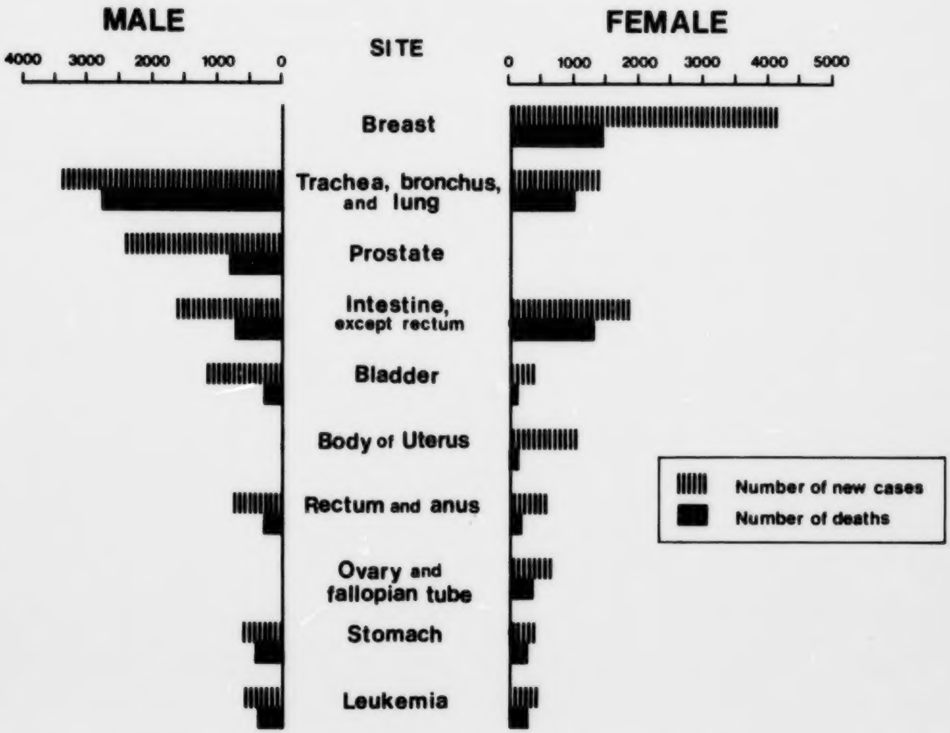

Fig. 1 New cases of, and deaths due to, malignant neoplasms, by sex and site of disease, for common cancers, Ontario 1983.

TABLE III

Age-adjusted Rates[1] and Cumulative Risks (age 0-74)[2], Incidence (I) and Mortality (M) from Malignant Neoplasms in Males, by Site and Age, Ontario, 1983

SITE OF DISEASE	ICD9[3] NUMBER	INCIDENCE/ MORTALITY	AGE AT DIAGNOSIS/DEATH (YEARS)							
			0-14	15-29	30-44	45-59	60-74	75+	All Ages	0-74
Lip and oral cavity	140-145	I	0.0	0.5	3.8	20.5	51.4	82.0	10.2	1.20
		M	0.0	0.0	0.3	3.8	14.4	31.2	2.5	0.30
Pharynx	146-148	I	0.1	0.1	1.4	9.4	17.2	12.6	3.5	0.42
		M	0.0	0.0	0.4	2.8	8.0	6.5	1.3	0.17
Esophagus	150	I	0.0	0.0	0.9	5.6	27.3	38.1	4.2	0.53
		M	0.0	0.0	0.4	5.7	31.9	49.6	4.8	0.61
Stomach	151	I	0.0	0.3	3.0	16.4	64.0	148.4	11.8	1.31
		M	0.0	0.2	1.4	9.9	42.6	122.0	8.1	0.87
Intestine, except rectum	152,153	I	0.1	0.5	6.3	41.5	173.2	383.2	30.8	3.57
		M	0.0	0.1	3.2	15.0	73.9	217.4	13.8	1.49
Rectum and anus	154	I	0.1	0.2	2.4	22.1	80.1	161.8	14.3	1.68
		M	0.0	0.0	0.4	6.5	32.1	83.3	5.6	0.64
Pancreas	157	I	0.0	0.1	1.9	12.3	53.2	93.5	8.9	1.07
		M	0.0	0.1	1.2	11.1	49.7	105.4	8.5	1.00
Larynx	161	I	0.0	0.0	1.5	15.7	40.7	34.2	7.0	0.92
		M	0.0	0.0	0.4	2.8	11.4	13.4	1.8	0.24
Trachea, bronchus and lung	162	I	0.0	0.3	8.6	107.4	401.5	578.3	65.4	7.94
		M	0.0	0.1	6.1	84.9	326.7	554.0	54.3	6.56
Bone	170	I	0.9	1.7	0.8	2.2	3.4	4.0	1.6	0.14
		M	0.2	0.2	0.5	0.3	0.8	1.1	0.5	0.04
Malignant melanoma of skin	172	I	0.2	2.3	8.4	17.4	27.2	34.5	7.9	0.86
		M	0.0	0.5	1.9	5.0	7.5	9.4	2.1	0.23
Prostate	185	I	0.0	0.0	0.4	22.4	266.5	852.8	44.5	4.84
		M	0.0	0.0	0.1	4.1	69.5	394.0	14.8	1.28
Testis	186	I	0.3	6.4	6.9	4.2	2.2	6.0	3.9	0.30
		M	0.1	0.4	0.6	0.6	0.5	1.1	0.4	0.03
Bladder	188	I	0.1	0.8	5.3	31.3	127.1	265.8	22.7	2.66
		M	0.0	0.0	0.3	3.1	23.2	111.6	4.8	0.46
Kidney and other urinary	189	I	1.1	0.0	3.0	18.3	40.9	59.5	8.5	1.00
		M	0.2	0.0	0.7	7.4	20.5	37.9	3.9	0.46
Brain and other nervous system	191,192	I	4.2	3.6	5.9	13.2	29.5	33.4	8.5	0.87
		M	0.5	1.1	2.8	8.5	23.8	29.6	5.0	0.55
Thyroid gland	193	I	0.0	0.4	1.9	2.9	5.9	3.7	1.5	0.17
		M	0.0	0.0	0.0	0.3	1.2	4.7	0.2	0.02
Lymphosarcoma and reticulosarcoma	200	I	0.4	1.1	2.3	11.4	27.2	48.5	5.9	0.66
		M	0.3	0.3	0.5	4.0	7.4	14.7	1.8	0.20
Hodgkin's disease	201	I	1.4	5.6	4.2	3.4	6.4	7.5	3.8	0.32
		M	0.0	0.9	0.6	2.1	4.4	7.2	1.2	0.12
Other lymphomas	202	I	0.7	0.9	4.0	10.7	20.6	37.2	5.4	0.58
		M	0.3	0.8	1.0	5.7	14.4	44.1	3.5	0.37
Multiple myeloma	203	I	0.0	0.0	0.2	6.1	25.1	62.8	4.5	0.52
		M	0.0	0.1	0.1	2.8	16.1	36.0	2.6	0.32
Leukemia	204-208	I	6.0	2.4	4.9	11.8	49.2	119.8	11.9	1.18
		M	2.2	1.8	2.7	5.6	26.2	67.8	6.2	0.62
ALL SITES[4]	140-208[4]	I	19.9	31.1	85.3	448.7	1,673.8	3,362.9	314.5	30.51
		M	4.8	8.0	28.1	211.7	890.0	2,149.8	163.4	17.00

[1] Age-adjusted by the direct method to the World Standard Population (See Table VII), expressed per 100,000 persons.

[2] Cumulative risk approximate to the percent probability of a cancer diagnosis/death occurring by age 74 (Reference: Day NE. International Agency for Research on Cancer (IARC) Scientific Publication No. 15. pp. 443-52, 1976).

[3] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

[4] Excluding non-melanotic skin cancers (ICD9 number 173). Note that any individual sites not specifically included in the table are included in "ALL SITES".

TABLE IV

Age-adjusted Rates[1] and Cumulative Risks (age 0-74)[2], Incidence (I) and Mortality (M) from Malignant Neoplasms in Females, by Site and Age, Ontario, 1983

SITE OF DISEASE	ICD9[3] NUMBER	INCIDENCE/ MORTALITY	AGE AT DIAGNOSIS/DEATH (YEARS)							
			0-14	15-29	30-44	45-59	60-74	75+	All Ages	0-74
Lip and oral cavity	140-145	I	0.1	1.1	1.2	7.5	17.5	24.0	3.7	0.43
		M	0.0	0.0	0.5	1.8	3.7	8.8	0.9	0.09
Pharynx	146-148	I	0.1	0.3	0.7	3.8	4.5	4.1	1.3	0.15
		M	0.0	0.0	0.6	1.0	1.6	4.6	0.5	0.05
Esophagus	150	I	0.0	0.0	0.3	2.7	7.1	18.6	1.5	0.17
		M	0.0	0.0	0.1	1.7	7.5	22.0	1.4	0.16
Stomach	151	I	0.0	0.3	1.6	9.5	24.8	83.0	5.7	0.58
		M	0.0	0.4	1.0	5.5	14.3	60.2	3.6	0.35
Intestine, except rectum	152,153	I	0.0	1.1	7.8	41.2	140.2	324.4	27.0	3.04
		M	0.0	0.1	2.2	15.3	56.6	159.2	11.0	1.21
Rectum and anus	154	I	0.0	0.4	2.5	16.5	43.8	90.3	8.8	0.99
		M	0.0	0.0	0.4	3.2	12.3	43.6	2.5	0.26
Pancreas	157	I	0.0	0.0	0.9	8.5	32.3	62.0	5.6	0.69
		M	0.0	0.0	1.0	7.7	31.4	59.9	5.4	0.68
Larynx	161	I	0.0	0.0	0.6	2.3	5.0	3.0	0.9	0.11
		M	0.0	0.0	0.0	0.8	1.6	1.5	0.3	0.03
Trachea, bronchus and lung	162	I	0.0	0.9	7.3	54.5	127.9	111.4	23.5	2.97
		M	0.0	0.2	3.9	35.5	96.7	97.2	16.7	2.10
Bone	170	I	1.4	1.3	0.4	0.5	3.0	3.2	1.3	0.10
		M	0.1	0.3	0.4	0.2	0.6	0.7	0.3	0.02
Malignant melanoma of skin	172	I	0.4	3.8	13.3	20.3	18.5	20.5	8.6	0.85
		M	0.0	0.6	1.6	4.2	3.1	7.7	1.5	0.14
Breast	174	I	0.0	2.2	58.5	182.0	282.9	356.2	71.0	7.76
		M	0.0	0.2	13.6	54.5	113.0	156.7	24.0	2.77
Cervix uteri	180	I	0.0	3.5	15.4	18.6	25.3	22.1	9.1	0.93
		M	0.0	0.2	3.9	8.3	13.1	25.9	3.7	0.41
Other uterus	179,181,182	I	0.0	0.7	7.3	43.6	102.0	68.2	18.6	2.34
		M	0.0	0.0	0.5	5.4	18.5	31.5	3.2	0.39
Ovary & other uterine adnexa	183	I	0.1	3.1	8.6	27.4	43.8	49.9	11.3	1.28
		M	0.1	0.3	1.7	13.7	31.2	41.9	6.1	0.73
Bladder	188	I	0.0	0.2	1.6	12.8	31.5	66.2	6.4	0.75
		M	0.0	0.0	0.2	1.5	6.2	31.4	1.5	0.14
Kidney and other urinary	189	I	1.4	0.2	1.8	7.9	18.6	30.7	4.3	0.48
		M	0.1	0.1	0.7	2.5	11.5	15.6	1.9	0.22
Brain and other nervous system	191,192	I	4.2	1.9	4.5	9.7	17.6	14.9	5.9	0.58
		M	1.5	0.7	2.2	6.3	12.5	10.9	3.3	0.35
Thyroid gland	193	I	0.4	3.2	7.2	7.3	7.5	8.5	4.1	0.40
		M	0.0	0.0	0.0	0.3	1.7	7.3	0.3	0.03
Lymphosarcoma and reticulosarcoma	200	I	0.2	0.7	2.9	7.8	16.5	32.3	4.1	0.45
		M	0.0	0.1	0.6	1.5	5.6	8.7	1.0	0.12
Hodgkin's disease	201	I	0.3	3.5	2.5	2.4	3.6	3.2	2.2	0.19
		M	0.0	0.5	1.2	0.5	0.7	3.5	0.6	0.04
Other lymphomas	202	I	0.3	0.7	3.1	8.5	16.0	19.9	3.9	0.45
		M	0.1	0.2	0.4	4.5	11.9	26.7	2.4	0.27
Multiple myeloma	203	I	0.0	0.0	0.6	3.8	16.6	30.2	2.8	0.35
		M	0.0	0.0	0.4	2.1	9.3	22.2	1.7	0.20
Leukemia	204-208	I	4.3	3.3	3.8	7.7	30.2	63.9	8.0	0.77
		M	1.9	1.1	3.5	6.1	16.1	44.6	4.7	0.46
ALL SITES[4]	140-208[4]	I	16.0	35.3	161.5	538.9	1,124.1	1,745.4	259.8	25.48
		M	4.2	4.9	43.5	198.3	540.3	1,056.3	110.9	11.84

[1] Age-adjusted by the direct method to the World Standard Population (See Table VII), expressed per 100,000 persons.

[2] Cumulative risk approximate to the percent probability of a cancer diagnosis/death occurring by age 74 (Reference: Day NE, International Agency for Research on Cancer (IARC) Scientific Publication No. 15, pp. 443-52, 1976).

[3] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

[4] Excluding non-melanotic skin cancers (ICD9 number 173). Note that any individual sites not specifically included in the table are included in "ALL SITES".

receiving the diagnosis of lung cancer by age 74. Of course, if age-specific rates continue to rise, the cumulative risk will increase also.

Cancer Mortality, 1984

The most current cancer mortality data are for 1984; these were provided by the Office of the Registrar-General of Ontario. Figs. 2 and 3 show the frequencies of death due to malignant neoplasms of all types relative to other major groups of causes of death. Tables V and VI give the numbers of cancer deaths by age group at death and site; the same format and groupings are used in Tables I and II for cancer incidence.

Populations

Table VII shows sex- and age-specific population data for Ontario for the years 1983 and 1984, and for the "world". The 1983 and 1984 Ontario populations, which are postcensal estimates, are provided for those who would like to calculate age-specific cancer incidence and mortality rates from data tabulated in the previous sections. The world population is an artificial standard, frequently used in the calculation of age-adjusted rates. The Ontario population data are provided by Statistics Canada, and the world population is taken from *Cancer Incidence in Five Continents*.

CANCER TREATMENT

Hospital Caseload

During the Ontario Ministry of Health's fiscal year 1983-84, there were 69,240 separations (discharges and deaths) from active and rehabilitation hospitals in Ontario in which the primary diagnosis was cancer. These accounted for 5.3% of all hospital separations and 1,067,626 days of hospital care. The average length of stay for cancer patients declined from 16.9 days in 1972 to 15.4 days in 1983-84*.

New Cancer Registrations

In the last decade, the number of new cases registered at the regional cancer centres and the OCI/PMH has increased by 44% from 14,125 cases to 20,315 (Table VIII). The Toronto-Bayview Centre, which opened in 1980, recorded the greatest increase in the number of cancers registered. To assess the significance of these changes over time, one must take into account the introduction in 1979 of the *International Classification of Diseases, Ninth Revision*, which separated the categories -- in situ carcinoma and neoplasms of uncertain behaviour -- from malignant neoplasms. In

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*Hospital Statistics 1983-84 published by the Ontario Ministry of Health.

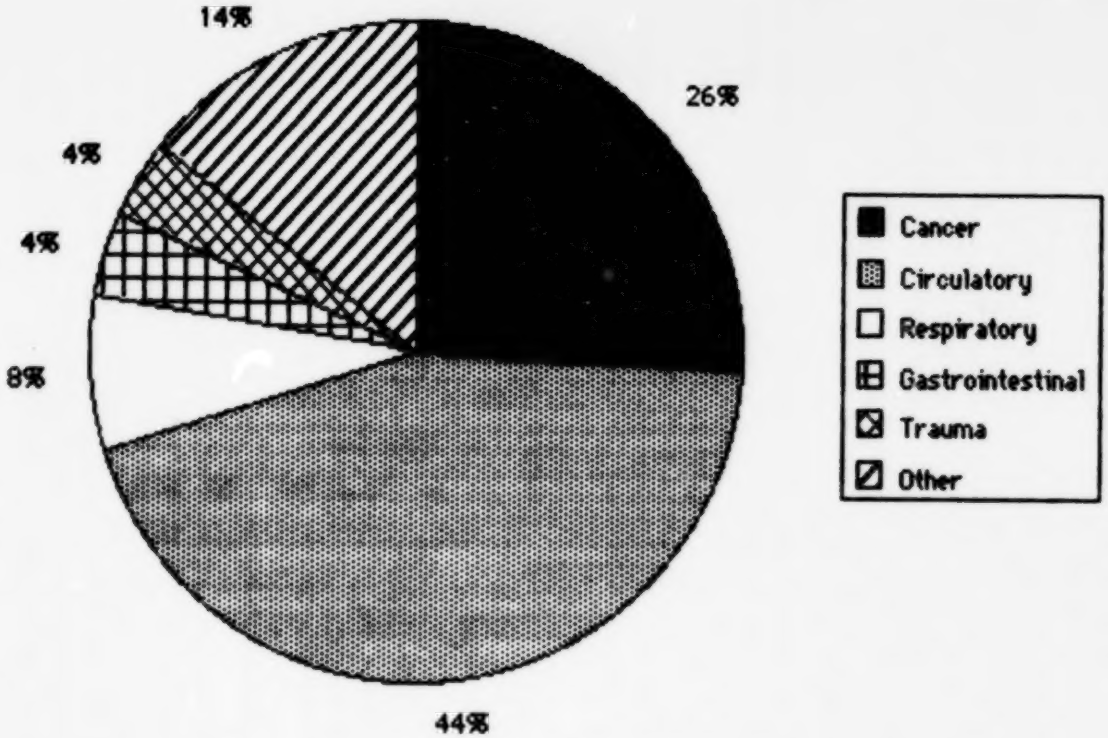

Fig. 2 Percentage distributions of major causes of death in males, Ontario 1984.

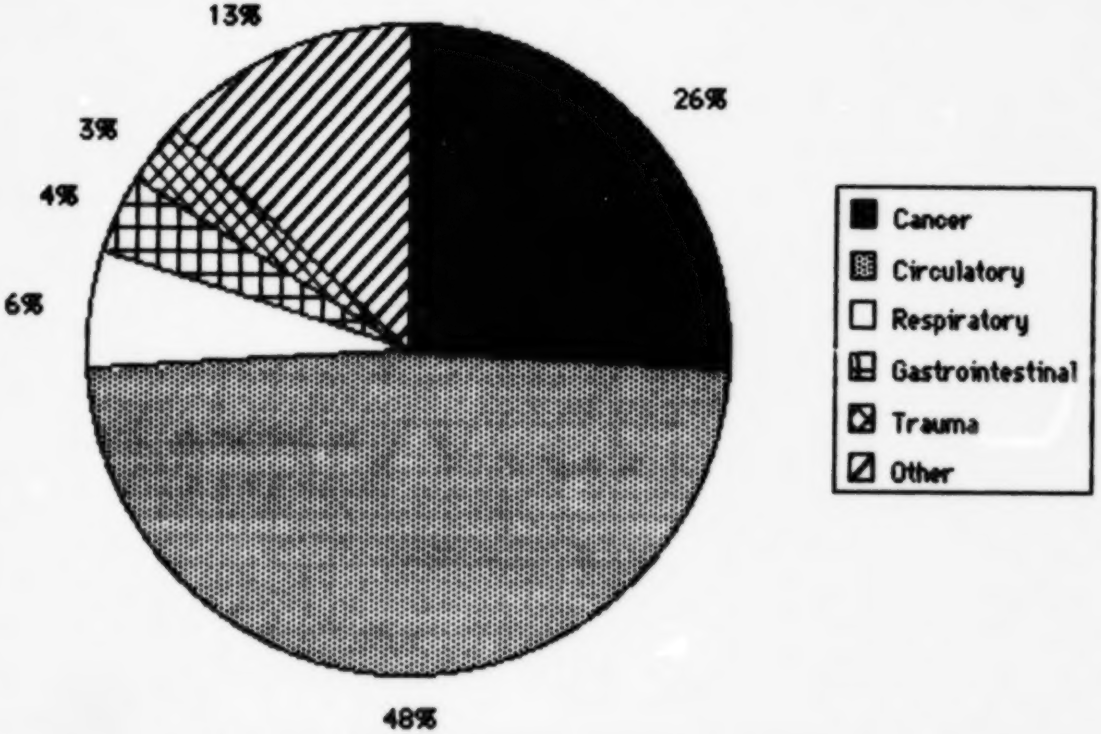

Fig. 3 Percentage distributions of major causes of death in females, Ontario 1984.

TABLE V

Number of Deaths due to Malignant Neoplasms in Males, by Site of Disease and Age at Death, Ontario 1984

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DEATH (YEARS)																	RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	All Ages	
Lip and oral cavity	140-145	0	0	0	0	0	1	2	0	1	5	8	20	16	17	19	34	123	14
Pharynx	146-148	0	0	0	0	0	0	0	0	1	3	9	5	17	9	7	7	58	
Esophagus	150	0	0	0	0	0	1	1	1	4	10	12	21	32	46	37	55	220	10
Stomach	151	0	0	0	0	0	0	0	5	9	10	28	42	71	98	79	156	498	4
Intestine, except rectum	152,153	0	0	0	0	2	2	2	3	12	20	37	64	116	98	146	273	775	3
Rectum and anus	154	0	0	0	0	0	1	1	4	3	4	16	33	33	45	51	95	286	7
Pancreas	157	0	0	0	0	0	2	2	4	3	13	26	41	74	79	79	125	448	5
Nasal cavities, middle ear and accessory sinuses	160	0	0	0	0	0	0	1	1	0	3	2	0	0	0	3	1	11	
Larynx	161	0	0	0	0	0	0	0	0	0	3	4	13	26	21	21	29	117	
Trachea, bronchus and lung	162	0	0	0	0	0	2	1	14	22	84	187	346	516	535	528	732	2,967	1
Bone	170	0	1	0	2	1	0	1	0	0	1	0	1	1	1	4	5	18	
Connective tissue	171	1	0	0	1	1	3	2	3	4	2	5	2	5	4	5	8	46	
Malignant melanoma of skin	172	0	0	0	1	1	2	5	2	9	7	10	9	14	9	9	20	98	
Breast	175	0	0	0	0	0	0	0	0	1	0	0	1	2	2	1	5	12	
Prostate	185	0	0	1	0	0	0	0	0	1	1	9	25	51	77	143	503	811	2
Testis	186	0	0	0	0	3	7	5	2	2	2	1	3	0	0	2	0	27	
Bladder	188	0	0	0	0	0	0	0	0	0	5	10	19	28	34	50	136	282	8
Kidney and other urinary	189	0	0	0	0	0	0	1	3	8	6	16	24	36	36	32	45	207	11
Brain and other nervous system	191,192	1	6	1	4	6	7	3	12	11	23	27	29	38	37	31	33	269	9
Thyroid gland	193	0	0	0	0	0	0	0	0	0	1	1	0	1	2	1	4	10	
Lymphosarcoma and reticulosarcoma	200	0	0	0	1	2	0	0	2	4	1	1	6	12	10	6	25	70	
Hodgkin's disease	201	0	0	0	0	5	7	5	5	3	5	2	3	3	3	4	10	55	
Other lymphomas	202	0	0	0	2	1	3	4	2	5	4	8	15	23	30	41	57	195	12
Multiple myeloma	203	0	0	0	0	0	0	0	2	1	2	12	12	24	18	24	52	147	13
Leukemia	204-208	3	5	8	6	6	6	12	9	9	9	12	28	36	27	50	101	327	6
Other and non-specific	Residual	6	0	3	0	6	3	8	11	13	31	46	90	122	119	147	261	866	
TOTAL	140-208[3]	11	12	13	17	34	47	56	85	126	255	489	852	1,297	1,317	1,520	2,772	8,903	

[1] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

[2] Rank order for sites with more than 100 deaths.

[3] Omitted are 37deaths due to non-melanotic cancer of the skin (ICD9 number 173).

TABLE VI

Number of Deaths due to Malignant Neoplasms in Females, by Site of Disease and Age at Death, Ontario 1984

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DEATH (YEARS)																	RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	All Ages	
Lip and oral cavity	140-145	0	0	0	0	0	0	0	1	0	0	7	6	6	11	5	21	57	
Pharynx	146-148	0	0	0	0	1	0	0	1	0	1	3	4	3	4	4	6	27	
Esophagus	150	0	0	0	0	0	0	0	2	1	4	2	8	9	16	13	46	101	16
Stomach	151	0	0	0	0	0	1	2	3	3	7	10	13	24	32	47	135	277	7
Intestine, except rectum	152,153	0	0	0	0	0	0	4	14	9	23	38	65	77	100	122	409	861	3
Rectum and anus	154	0	0	0	1	0	2	2	4	0	5	8	17	21	25	27	87	199	8.5
Pancreas	157	0	0	0	0	0	0	2	1	2	5	10	30	42	44	67	172	375	5
Nasal cavities, middle ear and accessory sinuses	160	0	0	0	0	0	0	0	0	1	0	0	2	0	1	0	3	7	
Larynx	161	0	0	0	0	0	0	0	0	0	2	0	4	2	5	5	8	26	
Trachea, bronchus and lung	162	0	0	0	0	0	0	3	9	24	52	106	152	174	178	189	254	1,141	2
Bone	170	1	0	2	1	1	2	0	1	0	0	0	0	0	1	1	5	15	
Connective tissue	171	1	0	0	1	0	2	0	2	1	0	2	3	4	3	2	15	36	
Malignant melanoma of skin	172	0	0	1	0	1	3	5	2	7	4	7	4	6	3	7	14	64	
Breast	174	0	0	0	0	1	4	11	41	61	99	153	191	218	188	195	410	1,572	1
Cervix uteri	180	0	0	0	0	1	4	8	17	15	12	9	22	21	19	18	48	194	10
Other uterus	179,181,182	0	0	0	0	0	1	0	0	2	3	2	10	33	29	35	77	192	11
Ovary and fallopian tube	183	0	0	1	0	2	0	2	7	13	13	38	44	78	67	53	107	425	4
Bladder	188	0	0	0	0	0	0	1	0	2	1	3	9	4	16	16	83	135	14
Kidney and other urinary	189	0	3	0	0	1	1	2	0	0	2	7	21	18	17	19	44	136	13
Brain and other nervous system	191,192	6	4	5	2	1	4	4	9	12	11	18	19	26	22	21	35	199	8.5
Thyroid gland	193	0	0	0	0	0	0	0	0	0	2	0	2	1	4	9	11	29	
Lymphosarcoma and reticulosarcoma	200	0	0	0	0	1	0	1	1	2	2	1	4	7	4	8	26	57	
Hodgkin's disease	201	0	0	0	0	3	3	4	2	0	0	2	2	8	4	6	6	40	
Other lymphomas	202	0	0	0	0	0	0	1	7	4	5	6	9	15	22	19	64	152	12
Multiple myeloma	203	0	0	0	0	0	0	0	0	2	4	3	4	16	15	13	58	115	15
Leukemia	204-208	2	4	4	8	5	7	3	6	10	8	9	12	27	23	50	101	279	6
Other and non-specific	Residual	5	3	1	3	0	3	5	8	10	21	25	62	93	101	133	404	877	
TOTAL	140-208[3]	15	14	14	16	18	37	60	138	181	286	469	719	933	955	1,084	2,649	7,588	

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[1] ICD9: International Classification of Diseases, Ninth Revision. World Health Organization, Geneva, 1977.
[2] Rank order for sites with more than 100 deaths.
[3] Omitted are 17 deaths due to non melanotic cancer of the skin (ICD9 number 173).

TABLE VII

World Standard Population and Estimated Population 1983 and 1984, of Ontario (In Thousands)

AGE GROUP	WORLD STANDARD[1]	ONTARIO, 1983[2]		ONTARIO, 1984[2]	
	MALE OR FEMALE	MALE	FEMALE	MALE	FEMALE
0-4	12.0	308.7	294.8	316.4	302.9
5-9	10.0	309.2	294.2	309.1	294.4
10-14	9.0	340.9	322.5	336.3	317.8
15-19	9.0	386.1	367.5	370.5	352.9
20-24	8.0	411.2	408.9	423.6	416.1
25-29	8.0	373.9	389.4	383.7	396.4
30-34	6.0	352.2	364.9	357.0	371.5
35-39	6.0	327.9	328.7	341.2	343.8
40-44	6.0	264.1	262.8	274.1	272.6
45-49	6.0	235.5	232.3	239.0	237.1
50-54	5.0	237.1	233.6	236.3	233.3
55-59	4.0	221.0	234.7	222.6	233.1
60-64	4.0	187.7	210.3	197.0	221.6
65-69	3.0	142.3	167.0	141.4	167.2
70-74	2.0	109.1	139.6	113.5	144.0
75+	2.0	128.6	228.7	133.5	237.6
TOTAL	100.0	4,335.5	4,479.9	4,395.2	4,542.3

[1] Waterhouse, John et al (eds). Cancer Incidence in Five Continents, Vol IV. World Health Organization, Geneva, 1982, p.673.

[2] Source: Statistics Canada.

TABLE VIII*

New Cancer Cases Registered by Treatment Centre, 1975-1984[1][2]

CENTRE	YEAR OF REGISTRATION									
	1975	1976	1977	1978	1979	1980	1981	1982*	1983	1984
Hamilton	2,091	2,254	2,353	2,493	2,594	2,507	2,537	2,688	2,780	2,782
Kingston	921	916	988	1,040	999	984	997	1,073	1,226	1,195
London	2,359	2,460	2,344	2,488	2,537	2,583	2,529	2,563	2,748	2,950
Ottawa	1,525	1,631	1,759	1,902	1,997	2,078	2,190	2,248	2,573	2,847
Thunder Bay	313	399	365	412	369	401	462	444	435	506
Toronto-Bayview	—	—	—	—	—	441	504	816	1,251	1,826
Toronto, PMH	6,027	6,158	6,462	6,960	6,911	7,057	7,320	7,012	7,332	7,171
Windsor	889	880	843	854	898	813	907	858	960	1,038
TOTAL	14,125	14,698	15,114	16,149	16,305	16,864	17,446	17,702	19,305	20,315

*Provisional (transition period — see text)

[1] Excludes carcinoma of cervix in situ.

[2] Any case registered at more than one treatment centre in a given year is allocated to the centre where it was first registered.

addition, in 1981, the Foundation returned to the international practice of counting patients with skin cancer as having only two lesions -- basal-cell or squamous-cell cancer -- and not as having multiple cancers of the same histology in different body sites. The distribution by cancer centre of the numbers of in situ lesions, neoplasms of uncertain behaviour and multiple skin cancers is shown at the foot of Table IX.

This increase in the number of cases seen at the regional cancer centres can be attributed in part to the greater occurrence of cancer in the population during the last decade. This increase represents a combination of an increase in population in Ontario, which is also aging, and an increase in smoking-related cancers. These trends will continue each year, with an expected annual increase in the absolute number of new cases of cancer requiring treatment.

In Table IX, for 1984, the major sites of newly registered cancers at these centres were lung, bronchus and trachea (16.4%), and breast (16.1%), followed by non-melanoma skin (11.3%). Of the 18,588 cancers seen for the first time at one of the regional cancer centres or the OCI/PMH, 14.2% were seen in Hamilton, 5.5% in Kingston, 13.9% in London, 14.0% in Ottawa, 2.5% in Thunder Bay, 9.0% at Toronto-Bayview, 4.0% in Windsor, and 36.0% at the Princess Margaret Hospital.

It should be noted that a "new case" registered at a Foundation's regional cancer centre refers to a case of cancer seen for the first time during that year at any one of the Foundation centres. If a case is seen at two cancer centres in the same year, the case is recorded as seen only by the first centre (1.7%) of cases were seen at more than two centres in the same year).

Almost 45% of all incident cases in the Province are referred at some time either to the regional cancer centres or the OCI/PMH; the proportion varies by site. Of incident cases in 1982, sites in which more than 70% of cases are seen by 1983 include cancer of the larynx, cancer of the cervix, cancer of the testis, and Hodgkin's disease (Table X). More than 50% of the most common tumors, cancers of the lung and breast, are referred to these centres. It should be noted that skin cancer, other than malignant melanoma of the skin, is not included in the provincial incidence cancer registry. This table uses incidence data for 1982 rather than 1983 because the earlier year gives a better reflection of referral patterns. Approximately 75% of cases are referred to the regional cancer centres and the OCI/PMH in the same year as they are diagnosed and almost 13% have been diagnosed in the previous year. Less than 5% have been diagnosed more than five years before being first referred.

The location of the peripheral clinics associated with the regional cancer centres and the OCI/PMH, and the type of outreach program, determine the referral pattern to each (Table XI). Thus, in Wentworth County, of the 1038 cases resident in the county, 1021 were referred to the Hamilton Centre and only a small number to other centres. On the other hand, in Waterloo County, of the 410 cases resident in Waterloo County, 225 were referred to the London Centre, 100 to the Hamilton Centre, 80 to the OCI/PMH and 5 were referred to the Toronto-Bayview Centre. From the Province of Quebec, 470 residents were referred to Foundation centres; most were seen at the Ottawa Centre. Additional 132 residents of other provinces

TABLE IX*

New Cancer Cases Registered by Site of Disease and Treatment Centre 1984

SITE OF DISEASE	ICD9[1] NUMBER	TREATMENT CENTRE								TOTAL	
		Hamilton	Kingston	London	Ottawa	Thunder Bay	Toronto		Windsor	Number	Per Cent
							Bayview	PMH			
Lip	140	17	10	18	13	6	5	26	11	106	0.6
Tongue	141	17	8	29	26	5	18	66	8	177	0.9
Rest of mouth	142-145	34	12	40	37	1	33	138	17	312	1.7
Pharynx and tonsil	146-149	39	13	23	46	7	31	122	19	300	1.6
Esophagus	150	21	4	19	29	6	21	80	8	188	1.0
Stomach	151	36	12	27	31	10	22	82	12	232	1.2
Intestine, except rectum	152,153	109	22	125	166	25	67	222	60	796	4.3
Rectum and anal canal	154	107	29	65	86	16	41	281	38	663	3.6
Other digestive system	155-159	40	11	44	52	12	40	79	26	304	1.6
Nose, middle ear and accessory sinuses	160	4	2	6	9	2	4	27	—	54	0.3
Larynx	161	51	15	57	62	6	40	167	13	411	2.2
Lung, bronchus and trachea	162	382	202	411	398	95	349	1,071	145	3,053	16.4
Other respiratory	163-165	8	1	12	8	1	7	18	—	55	0.3
Bone	170	6	1	6	7	2	4	23	2	51	0.3
Malignant melanoma	172	55	12	35	79	3	106	138	30	458	2.5
Other cancer of skin	173	279	193	420	194	62	273	572	117	2,110	11.3
Breast	174,175	438	158	397	505	57	205	1,093	131	2,984	16.1
Cervix uteri	180	48	26	55	52	11	8	174	13	387	2.1
Other uterus	179,181,182	92	32	106	104	13	20	229	23	619	3.3
Ovary, tubes and ligament	183	66	30	69	62	14	17	188	14	460	2.5
Other female genital organs	184	18	1	15	14	1	5	33	5	92	0.5
Prostate	185	150	53	108	110	20	78	316	37	872	4.7
Testis	186	19	6	25	18	1	5	64	8	146	0.8
Other male genital organs	187	4	1	2	2	—	4	8	—	21	0.1
Bladder	188	72	20	59	67	14	31	157	29	449	2.4
Kidney and other urinary	189	47	13	28	27	10	21	82	11	239	1.3
Brain and nervous system	191,192	51	14	87	53	7	37	168	14	431	2.3
Thyroid gland	193	10	6	11	6	3	7	48	1	92	0.5
Lymphosarcoma and reticulum-cell sarcoma	200	38	14	50	46	12	29	184	14	387	2.1
Hodgkin's disease	201	36	19	27	37	5	16	114	6	260	1.4
Other lymphomas	202	67	12	42	66	7	22	123	12	351	1.9
Leukemia	204-208	62	22	41	36	7	6	167	44	385	2.1
Other sites	Residual	206	50	134	156	25	99	431	42	1,143	6.1
TOTAL		2,629	1,024	2,593	2,604	466	1,671	6,691	910	18,588	100.0
Cervix uteri (in situ)	233.1	1	3	4	8	—	—	12	4	32	. . .
Other sites (in situ)	230-234	30	16	52	45	10	43	72	17	285	. . .
Neoplasms of uncertain behaviour	235-238	21	4	28	17	2	7	50	16	145	. . .
Multiple skins (see text)	173	102	151	277	181	28	105	358	95	1,297	. . .

*Provisional (transition period — see text)

[1] ICD9 — International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

TABLE X*

Incident Cases of Cancer[1] Diagnosed in 1982 by Site of Disease and by Referral to Cancer Treatment Centre

SITE OF DISEASE	TREATMENT CENTRE								ALL CENTRES		TOTAL
	Hamilton	Kingston	London	Ottawa	Thunder Bay	Bayview	Toronto		Number	Per Cent	Cases Reported
							PMH	Windsor			
Lip	11	12	18	7	11	1	26	4	90	33.1	272
Tongue	10	5	11	16	1	14	56	5	118	74.2	159
Rest of mouth	26	9	32	24	3	22	101	11	228	69.9	326
Pharynx and tonsil	28	9	34	24	5	13	116	8	237	84.0	282
Esophagus	17	11	21	19	5	7	75	7	162	50.6	320
Stomach	28	6	25	25	20	15	62	14	195	20.4	955
Intestine, except rectum	59	25	61	90	64	28	145	28	500	14.9	3,348
Rectum and anal canal	70	21	44	44	30	21	213	17	460	34.6	1,328
Other digestive system	35	17	34	38	39	25	87	37	312	20.4	1,529
Nose, middle ear and accessory sinuses	6	5	7	4	—	5	22	1	50	66.7	75
Larynx	40	19	33	24	10	19	151	9	305	79.0	386
Lung, bronchus and trachea	313	156	275	234	106	128	1,022	139	2,373	52.4	4,526
Other respiratory	10	3	7	5	1	3	17	—	46	50.5	91
Bone	8	2	5	4	1	3	16	1	40	37.4	107
Malignant melanoma	54	18	24	42	7	75	106	8	334	39.9	837
Breast	293	98	275	274	84	54	777	115	1,970	50.5	3,902
Cervix uteri	43	12	38	31	14	3	174	9	324	72.0	450
Other uterus	94	41	100	76	15	4	200	23	553	52.3	1,053
Ovary, tubes and ligament	60	22	31	35	12	4	180	17	361	55.4	651
Other female genital organs	11	9	6	9	—	—	20	1	56	40.9	137
Prostate	70	37	58	46	53	22	193	11	490	20.5	2,387
Testis	14	4	11	14	3	—	80	8	134	79.8	168
Other male genital organs	1	—	2	2	—	1	4	—	10	19.6	51
Bladder	57	23	46	30	29	9	137	21	352	22.3	1,575
Kidney and other urinary	28	8	30	24	19	11	68	8	196	30.4	644
Brain and nervous system	37	11	58	38	14	28	159	10	355	53.8	660
Thyroid gland	9	1	7	4	8	4	32	1	66	25.7	257
Lymphosarcoma and reticulum-cell sarcoma	51	15	47	38	11	20	151	11	344	59.8	575
Hodgkin's disease	25	13	26	24	6	13	104	12	223	73.3	300
Other lymphomas	59	18	24	34	6	10	72	7	230	46.5	495
Leukemia	50	16	40	25	19	6	103	29	288	28.6	1,005
Other sites	75	21	69	64	23	35	242	27	556	29.0	1,918
TOTAL	1,692[1]	667	1,499	1,368	619	603	4,911	599	11,958	38.9	30,769

*Provisional (transition period — see text).

[1] Excludes skin cancer (ICD9 number 173).

TABLE XI*

New Cancer Cases Registered by Place of Residence and Treatment Centre, 1984

COUNTY OR DISTRICT	TREATMENT CENTRE								TOTAL
	Hamilton	Kingston	London	Ottawa	Thunder Bay	Toronto		Windsor	
						Bayview	PMH		
Algoma	1	2	5	2	2	2	130	2	146
Brant	198	—	12	1	—	—	11	—	222
Bruce	—	—	95	—	—	4	50	1	150
Carleton	3	2	—	1,359	1	3	13	—	1,381
Cochrane	1	5	1	11	2	8	124	—	152
Dufferin	3	—	—	—	—	2	40	—	45
Dundas	—	2	—	36	—	—	—	—	38
Durham²	—	—	—	—	—	60	297	—	357
Elgin	—	—	133	—	—	—	1	1	135
Essex	10	2	42	—	1	1	10	861	927
Frontenac	4	275	1	5	—	—	3	1	289
Glengarry	—	1	—	48	—	1	—	—	50
Grenville	—	36	—	35	—	1	2	—	74
Grey	5	4	66	—	—	5	121	—	201
Haldimand-Norfolk³	141	—	62	—	—	—	3	1	207
Haliburton	2	—	—	—	—	3	24	—	29
Halton	294	—	2	2	—	11	173	—	482
Hastings	2	219	—	9	—	9	65	—	304
Huron	3	—	123	—	—	—	1	—	127
Kenora	2	1	2	—	23	—	1	—	29
Kent	—	1	240	—	—	2	3	21	267
Lambton	—	—	270	—	—	2	5	1	278
Lanark	—	45	4	96	—	1	—	—	146
Leeds	—	150	1	9	—	—	—	—	160
Lennox and Addington	—	78	—	3	—	—	1	—	82
Manitoulin	—	—	—	1	—	—	23	—	24
Middlesex	7	1	840	3	—	—	8	2	861
Muskoka	1	1	—	—	—	13	82	—	97
Niagara¹	571	—	4	—	—	24	166	—	765
Nipissing	—	—	2	13	—	2	156	1	174
Northumberland²	—	27	—	—	—	13	84	—	124
Oxford	5	—	219	—	—	—	1	—	225
Parry Sound	2	2	—	2	—	4	81	—	91
Peel	10	—	—	1	—	43	596	1	651
Perth	3	—	136	2	—	—	9	—	150

TABLE XI* (Continued)

New Cancer Cases Registered by Place of Residence and Treatment Centre, 1984

COUNTY OR DISTRICT	TREATMENT CENTRE								TOTAL
	Hamilton	Kingston	London	Ottawa	Thunder Bay	Toronto		Windsor	
						Bayview	PMH		
Peterborough[2]	2	3	2	1	—	17	196	—	221
Prescott	—	—	—	60	—	—	1	—	61
Prince Edward	—	67	—	—	—	2	1	—	70
Rainy River	—	1	—	—	32	3	—	—	36
Renfrew	—	—	—	201	—	1	6	—	208
Russell	—	—	—	42	—	1	1	—	44
Simcoe[2]	2	—	3	2	—	111	379	—	497
Stormont	—	13	—	137	—	—	—	—	150
Sudbury	4	—	—	14	—	6	326	2	352
Thunder Bay	2	—	3	1	397	3	29	—	435
Timiskaming	7	—	2	8	—	9	61	—	87
Victoria[2]	—	1	—	—	—	15	86	—	102
Waterloo	100	—	225	—	—	5	80	—	410
Wellington	166	2	32	—	—	4	37	—	241
Wentworth	1,021	—	—	—	—	6	11	—	1,038
York	9	2	2	1	—	1,217	3,033	2	4,266
Quebec	—	9	2	430	—	7	20	2	470
Other Provinces	14	10	8	15	5	8	67	5	132
U.S.A.	—	31	5	6	—	10	17	4	73
Other World	3	—	2	13	—	11	56	2	87
Residence at diagnosis not stated	31	31 31	47	35	3	21	—	—	168
TOTAL	2,629	1,024	2,593	2,604	466	1,671	6,691	910	18,588

*Provisional (transition period — see text).

[1] In 1971 the counties of Welland and Lincoln became the Regional Municipality of Niagara.

[2] In 1974 the counties of Durham and Ontario became the Durham Regional Municipality. Also the counties of Simcoe, Peterborough, Northumberland and Victoria have been expanded by parts of Durham and Ontario.

[3] In 1974 the counties of Haldimand and Norfolk became the Regional Municipality of Haldimand-Norfolk.

were in Ontario, principally at the OCI/PMH. Of the 160 residents of the USA and other countries treated in Ontario, most were seen at the OCI/PMH, and the Ottawa and Kingston Centres.

The data in Tables VIII through XI are marked "provisional", since implementation of the Patient Care Management System in the centres from which these are extracted, is not yet complete. However, we anticipate that the final data will differ only slightly from those presented here.

ACKNOWLEDGEMENTS

We acknowledge with gratitude the continuing co-operation of government. The Ontario Ministry of Health has provided source records and advice; the Office of the Registrar General of the Ministry of Consumer and Commercial Relations has provided computerized data on deaths due to all causes in Ontario residents and, in addition, has provided facilities for an on-site search of their records for treatment evaluation and other research. We appreciate the assistance of the staff of the Hospital Medical Records Institute (HMRI) and are indebted to the medical records staff of all hospitals in Ontario who willingly and promptly provide additional information, primarily for the generation of incidence data, but also to ensure the high quality of data entered in the cancer registry.

We extend a special thanks to the directors of the regional cancer centres and the OCI/PMH and their managers of health records for support during the year, and to the members of the Foundation's Standing Committee on Records and Statistics and its sub-committees.

We acknowledge with gratitude the assistance of all the staff of Information Systems in the processing of the Foundation's large data base. In particular, we thank the individuals working under the direction of Mrs. June Murphy and Mr. Tom Broz, who have generated incidence data up to and including 1983.

Our special thanks are extended to Mrs. Mary Nemes, Manager of Health Records in the Division, Miss Darlene Dale, Supervisor of Cancer Registry Records, and the staff of the Division for their dedication to the generation of incidence data and their continual effort to improve the quality of the Ontario Cancer Registry. We are also grateful to Mmes. Margaret Holman and Sheila Wing for their help in preparing this report and to the staff of the Epidemiology Research Unit at the University of Toronto.

INFORMATION SYSTEMS

UPDATE OF INFORMATION SYSTEMS

J.I. MURPHY, B.A.* *Toronto, Ontario*

Last year, *Cancer in Ontario* described the role of Information Systems within the Foundation and discussed computerized applications, which had been installed or were planned. Currently, this department is working to stabilize the present systems and to plan for future requirements. This "update" describes the changes that have taken place during the past year and comments on future developments.

Computer Hardware

In October 1985, a new Honeywell DPS 6/95 minicomputer was installed in Head Office and became the production computer system shared by the Toronto-Bayview Centre and the Division of Epidemiology and Statistics. The DPS 6/92 computer, which served this function in the past, was converted for use as a program development and testing machine. The DPS 6/48 computer, thus displaced, was shipped to the new Northeastern Ontario Oncology Program at the Laurentian Hospital in Sudbury and will be installed in early 1986. All centres added a third disk drive to their Honeywell computer. Three centres – Hamilton, London and Ottawa – had model upgrades to meet the increasing work load on the systems.

The IBM PC microcomputer continues to be popular and now we have over 100 PCs, which are used primarily for word processing and business office applications.

Computer Applications

Regional Cancer Centres. The centres have had no major new applications although we have completed the automation of chart tracking, OHIP billing and progress notes.

The centres now produce their own caseload and service load statistics. We are creating additional specialized workload programs to provide even more detailed information.

The centres once required assistance from Head Office staff to meet requests for listings of patients meeting special criteria, e.g., breast cancer patients between the ages of 45 and 55 who were diagnosed in the years 1980 to 1983. Now some of the most common types of information are available to authorized users directly through online entry of parameters in an easy-to-use prompted format. This facility is very popular and we are developing additional formats.

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*Manager, Information Systems, Ontario Cancer Treatment and Research Foundation.

The Foundation has acquired the MEDLOG system from Information Analysis Corporation for use in special studies. Running on the local area network of PCs, it allows users to define data fields and combine these fields into online data entry screens. Data can be input to MEDLOG using the defined screens; also they can be downloaded from the Honeywell system. MEDLOG offers a variety of tools for data analysis including survival analysis. For more complex analysis, data can be formatted for transport to more sophisticated systems such as SAS or SPSS. Dr. Mark Levine of the Hamilton Centre is chairman of a MEDLOG users' group, which is considering the development of a standard dictionary of data fields for all Foundation MEDLOG users.

At the 9th Annual Symposium for Computer Applications in Medical Care (SCAMC) in Baltimore in November, Mrs. June Murphy read papers on the Foundtion's computer systems and the progress note application. These papers were published in the proceedings of the symposium. In May, in Toronto, Mrs. Murphy also made a presentation at the 10th Conference of the Canadian Organization for the Advancement of Computers in Health (COACH). This paper provided an overview of computer applications within the Foundation.

Ontario Cancer Registry. In 1985 we completed four record linkages to generate the 1983 incidence data. The hospital discharge records and records for patients with a diagnosis of cancer were linked internally to bring together multiple admissions of the same patient. Pathology reports indicating a diagnosis of cancer were then linked to the hospital discharges to create a preliminary 1983 incidence file. Prevalent cases were identified by linking the preliminary incidence file with the previous incidence file, which contained cases up to 1982.

The following statistics indicate the size of the linkage process by identifying volumes associated with the linkage between the 1983 preliminary incidence file and the 1964-1982 incidence file:

Records in 1983 preliminary incidence file	73,892
Patients in 1964-1982 incidence file	407,125
Grey area links manually examined	6,162
Grey area links kept	3,028
Grey area links rejected	3,134
Prevalent cases	34,398

Data in this incidence file then was refined by a linkage with patient information from the Foundation's regional cancer centres and from the Ontario Cancer Institute.

In 1986, the staffs of the Division of Epidemiology and Statistics and of Information Systems propose to create standard linkages, which can be used to link research data bases to the Registry data base, thereby expanding the usefulness of the Registry.

The case resolution process, which follows the record linkage system, determines cases by analysis of all records brought together on a patient during linkage. This system was enhanced in 1985 to edit its results for incompatible combinations of site, sex, age and histology. Several versions of the program were created to apply various rules for determining multiple primaries in the same patient.

Cases identified by case resolution are processed by the rates system. In addition to age-specific and age-adjusted rates, the system now can be requested to calculate the standard mortality ratio (SMR), the standard incidence ratio (SIR), proportional mortality ratio (PMR), mortality incidence ratio, and person years of life lost (PYLL). All statistics can be computed for Ontario as a whole, or for specified geographic areas.

In August 1985, Tom Broz presented a paper, Record Linkage in Cancer Registration, to the 6th European Congress on Medical Information in Helsinki. He also presented a paper to SCAMC in Baltimore on Computerized Disease Determination in a Large Cancer Registry. Jill Chin described the case resolution process to the International Association of Cancer Registries meeting in Hartford, Connecticut, in December.

Financial and Administrative Systems. Recently, a subcommittee was formed with representatives from the regional cancer centres, Head Office Finance, and Information Systems to develop requirements for new computerized financial and administrative systems. This group is not expected to report before the end of 1986.

Services. In 1985, the Hotline facility, established to provide service to all system users, was significantly expanded. A problem identification and resolution tracking system (PIRTS) was created to handle questions and problems related to any of the Foundation's computerized systems. Problems are assigned a priority based upon the seriousness and inconvenience to the user.

In 1986, we hope to develop an on-line tracking system that will permit input and enquiry from various sources. It will also enable Hotline staff to determine immediately the status of a problem, spot problem patterns, and provide more feedback to users about present and potential problems.

A Quality Assurance group has been established in Information Systems to safeguard the integrity and security of the Foundation's data, and the performance and quality of all systems' programs. A series of analysis tools have been developed to monitor the data bases. Security measures are being implemented to guarantee the safety of all data and to ensure that only authorized persons have access to information.

Major objectives of this group include the identification and maintenance of standards for system programs, system documentation and user documentation. Also included are control procedures and audits for production, operations and data control.

The Quality Assurance group arranged a two-day workshop for co-ordinators from all the centres. This provided them with an opportunity to review operating procedures, discuss any problems, and to share information with their counterparts from the other centres. Because of their positive response, its sponsors plan to give this workshop twice each year.

Future Requirements

All regional cancer centres and Head Office departments are evaluating their future information systems requirements. With the aid of an external consultant, the Foundation's Committee on Information Systems will turn these requirements into an action plan for the next five years. It is hoped that this plan will be available by the fall of 1986.

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APPENDICES

APPENDIX A

BEQUESTS AND OTHER DONATIONS

The Foundation was the grateful recipient of legacies, bequests and other donations totalling $2,023,991 for the fiscal year ending March 31, 1985, which are of inestimable value to the Foundation's program.

Legacies of $1,000 or over were received during the above period from the following estates:

The late Annie M.S. Abbott, Toronto	$ 5,500	
– Bernadine Adams, Hamilton	6,094	
– Clifford George Auvache, London for use at London Centre	41,577	
– Mattie Helen Ball, St. Thomas for use at London Centre	11,485	
– Mildred Marion Ball, St. Thomas for use at London Centre	65,992	
– Robert Hugh Ball, Strathroy for research at London Centre	18,000	
– Rhano Mary Beamish, Kitchener	5,000	
– Mary Jane Bell, Toronto	2,000	
– Dr. Russell B. Birrell, Toronto for research	32,183	
– Allan Fitzherbert Bridges, Windsor for use at Windsor Centre	8,593	
– George Rae Browne, Toronto	39,000	
– Jessie Madge Browne, Toronto	200,000	(part)
– Bertha Jane Burnett, Toronto	1,000	
– Gertrude Lilian Calvello, North Bay	67,965	
– Kate Nelson Casseday, Toronto	2,000	
– Emily Jane Cooke, London for use at London Centre	9,744	
– R.C.M. Cree, Windsor	1,000	
– Joseph Chester Daley, Toronto	2,000	
– Alberta McNab Daly, Toronto	1,081	(part)
– David Collier Davidson, Scarborough	5,000	
– Elizabeth Davidson, Township of Wilmot, Municipality of Waterloo	101,953	

– Marion Dawson, Leamington	5,700
– Beecher Dennis, Toronto	4,000 (part)
– John MacKenzie Dow, Fullerton Township, Perth County	10,000 (part)
– Violet Mary Downey, Toronto	20,000 (part)
– Eldred Durham, Toronto (Anne and Eldred Durham Trust Fund) for research	9,286 (part)
– Clarence Henderson Ellis, Islington	2,000
– Annie Euler, Dryden for use at Amethyst House Lodge Thunder Bay	2,000
– Annie Edith Forester, Etobicoke	1,500
– John Jacob Freedman, Toronto	75,000 (part)
– Gertrude Lillian Garbutt, Toronto	150,000 (part)
– Hazel Norma Gilbert, London	36,000 (part)
– Harold James Goodman, London	1,000
– Ivy Mae Grabb, Hamilton	2,000
– Bertha Hogg, Toronto	9,397
– Marie Jeanne Hughes, Thunder Bay for use at Thunder Bay Centre	1,000
– Francis William Johnstone, Strathroy for research at London Centre	5,000
– William Jones, Oil Springs for research	52,463
– Mabel Matilda Kelley, London for use at London Centre	72,000
– Angeline Lecours, Hearst	5,000
– Frances Levine, Toronto	1,328
– Kathleen Loney, Mississauga	2,000
– Birdie Muriel Lounsbury, Brantford	1,162
– Edna Doris Lowe, Toronto	44,000 (part)
– Robert Byers McFarlane, London for use at London Centre	1,000
– Hugh Ignatius McGinty, West Flamborough	1,000
– Edith Doris McGregor, Welland	48,692
– Arvilla Marion McIntyre, Brampton	17,303
– Myrtle L. Montgomery, Etobicoke	1,000
– Ethel Herbertina Moore, Peterborough	1,000
– Ruby Elizabeth Morrison, Dutton	3,000
– Edith Pepper, Toronto	4,000
– Margaret Mary Rae, Ottawa for use at Ottawa Centre	1,000

– Eleanor Frances Raymer, Downsview	2,000	
– Henrietta Richardson, Toronto	3,938	
– Bertha M. Richter, London (Richter Endowment Fund Trust) in memory of Martha Ann Richter and George Richter for use at London Centre	186,000	(part)
– Mary Rosella Roach, Orillia	5,165	
– Marion Ross, Scarborough	1,000	
– Clara B. Sanderson, Brantford (John A. Sanderson and Family Trust)	8,581	(part)
– Mary Rose Sarrazin, Ottawa for use at Ottawa Centre	1,000	
– Don Gibson Shepard, Windsor for use at Windsor Centre	10,000	
– Ethel Anne Stewart, Ottawa for use at Ottawa Centre	41,477	
– Louisa A. Turner, Scarborough	12,000	(part)
– Christina Mary Urquhart, Cornwall for use at Ottawa Centre	7,656	
– Godfrey Bryant Webb, Toronto	21,726	
– Muriel Eva Whitworth, Lucan	5,523	
– Madeleine Wilson, St. Marys for research at London Centre	3,466	

Donations of $1,000 or more were received from the following:

– Ruth Armstrong, Oakville for research	1,000
– Atomic Energy of Canada Ltd., Ottawa for use in hyperthermia research at Ottawa Centre	1,419
– Karl Bald, Toronto for research at Toronto-Bayview Centre	1,000
– The Barrie Foundation, St. Thomas for use at London Centre and/or the University of Western Ontario	5,000
– Charles Bingley, Fonthill for research	1,000
– Irene Boulton, Windsor for research at Windsor Centre	1,000
– Peter E. Case, Toronto to furnish children's room in chemotherapy department at Kingston Centre	1,000

– James Dennett, Corunna for research at London Centre	1,000
– Dreams Never Die, Ottawa (softball tournament) for use at Ottawa Centre	3,250
– Hamilton Radiotherapy Associates Group Dr. R.G. MacLaren Memorial Fund	2,700
– Loyal Order of the Moose, London for palliative care at London Centre	1,000
– Jack Lynch, Windsor for purchase of furniture for use at Windsor Centre	1,544
– Mr. and Mrs. M. Manich, Thunder Bay for use at Thunder Bay Centre	1,000
– John Martin, Thunder Bay for cancer patients in Thunder Bay area	1,000
– Mercedes-Benz Canada Inc., Toronto for purchase of background music system at Toronto-Bayview Centre	4,578
– Edith Mutrie, Thornhill for research at Toronto-Bayview Centre	1,000
– Constance MacDougall, Caledon East for research at Toronto-Bayview Centre	1,000
– Mary MacLennan, Windsor for research	1,000
– Ottawa Civic Hospital, Ottawa to the Gordon Beattie Memorial Fund for use in the library	16,432
– S. Pefanis, Alexandria to furnish children's room in chemotherapy department at Kingston Centre	1,000
– Elsie Pratt, Barrie for use at Toronto-Bayview Centre	2,000
– St. Claire Ladies Club, Windsor for use at Windsor Centre	2,852
– Arthur Schneider, Brunner for research at London Centre	1,000
– Schwartz Foods Cookie Haus, Cambridge for use at Thameswood Lodge, London	1,000

– Joseph Schwartz, Cambridge for use at Thameswood Lodge, London	1,000
– Dr. A.H. Sellers, Toronto for visiting lecturer in cancer epidemiology	1,000
– Doreen Steinacker, Stratford for research at London Centre	1,000
– Thomas Thornton, Wiarton for use at Thameswood Lodge, London	1,000
– The Toronto Star, Toronto	1,000
– H.G. Vail Family Holdings Ltd., Ottawa for use in hyperthermia research at Ottawa Centre	10,000
– Workmen's Circle Social Club Willowdale, for research	5,000
– H. Wrigglesworth, Don Mills (Dorothy Wrigglesworth Cancer Research Fund)	1,000

The Foundation is grateful to these donors and to the many others not listed above and reveres the memory of those who extended their lifetime efforts to fight cancer when making their wills. These welcome additions to our research program can proceed at a time of financial constraints and inflated costs.

APPENDIX B

LIST OF ARTICLES PUBLISHED IN 1984 BY CAREER SCIENTISTS, RESEARCH ASSOCIATES, GRANTEES AND MEMBERS OF THE OCTRF STAFFS AT THE REGIONAL CANCER CENTRES AND HEAD OFFICE

HAMILTON

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JEEVES WP, RAINBOW AJ: UV-enhanced reactivation of UV- and gamma-irradiated adenovirus in xeroderma pigmentosum and Cockayne syndrome fibroblasts. *Int J Radiat Biol* 1983; **43:** 624.

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RAINBOW AJ, JEEVES WP, BENNETT CB, HOWES M: Abnormal enhanced reactivation and mutagenesis of UV-irradiated adenovirus in ataxia telangiectasia fibroblasts. *In:* Broerse JJ, Barendsen GW, Kal HB, Van der Kogel AJ, eds. Proceedings of the Seventh International Congress of Radiation Research. Amsterdam: Martinus Nijhoff Publishers, 1983: B4-30.

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KINGSTON

OCTRF Kingston Regional Cancer Centre:

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